

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
31 October 2002 (31.10.2002)

PCT

(10) International Publication Number  
**WO 02/085308 A3**

- (51) International Patent Classification<sup>7</sup>: **C07H 21/00**, (74) Agent: **AMZEL, Viviana**; EpiGenesis Pharmaceuticals, Inc., 7 Clarke Drive, Cranbury, NJ 08512 (US).  
C12Q 1/68
- (21) International Application Number: PCT/US02/13135 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, VZ, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 23 April 2002 (23.04.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/286,137 24 April 2001 (24.04.2001) US (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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- Published:  
— with international search report  
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments  
— with sequence listing part of description published separately in electronic form and available upon request from the International Bureau
- (88) Date of publication of the international search report:  
19 December 2002
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: ANTISENSE AND ANTI-INFLAMMATORY BASED COMPOSITIONS TO TREAT RESPIRATORY DISORDERS

(57) Abstract: A pharmaceutical composition and formulations comprise preventative, prophylactic or therapeutic amounts of an oligo(s) anti-sense to a specific gene(s) or its corresponding mRNA(s), and a glucocorticoid and/or non-glucocorticoid steroid or a ubiquinone or their salts. The agents, composition and formulations are used for treatment of ailments associated with impaired respiration, bronchoconstriction, lung allergy(ies) or inflammation, and abnormal levels of adenosine, adenosine receptors, sensitivity to adenosine, lung surfactant and ubiquinone, such as pulmonary fibrosis, vasoconstriction, inflammation, allergies, allergic rhinitis, asthma, impeded respiration, lung pain, cystic fibrosis, bronchoconstriction, COPD, RDS, ARDS, cancer, and others. The present treatment is effectively administered by itself for conditions without known therapies, as a substitute for therapies exhibiting undesirable side effects, or in combination with other treatments, e.g. before, during and after other respiratory system therapies, radiation, chemotherapy, antibody therapy and surgery, among others. Each of the agents of this invention may be administered directly into the respiratory system so that they gain direct access to the lungs, or by other effective routes of administration. A kit comprises a delivery device, the agents and instructions for its use.

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**COMPOSITIONS, FORMULATIONS & KIT WITH ANTI-SENSE  
OLIGONUCLEOTIDE & ANTI-INFLAMMATORY STEROID AND/OR UBIQUINONE  
FOR TREATMENT OF RESPIRATORY & LUNG DISEASE**

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**BACKGROUND OF THE INVENTION**

**Field of the Invention**

This invention concerns itself with compositions, formulations and kits employed for the administration of active agents that are effective for treating respiratory and pulmonary diseases including bronchoconstriction, impaired airways, decreased lung surfactant, asthma, rhinitis, acute respiratory distress syndrome (ARDS), infantile or maternal RDS, chronic obstructive pulmonary disease (COPD), allergies, impeded respiration, lung pain, cystic fibrosis (CF), infectious diseases, cancers such as leukemias, lung and colon cancer, and the like, and diseases whose secondary effects afflict the lungs. The active agents, anti-sense oligonucleotides and steroid agents and/or ubiquinones may be administered preventatively, prophylactically or therapeutically as a single therapy or in conjunction with other therapies.

**Background of the Invention**

Respiratory ailments, associated with a variety of diseases and conditions, are extremely common in the general population, and more so in certain ethnic groups, such as African Americans. In some cases they are accompanied by inflammation, which aggravates the condition of the lungs. Asthma, for example, is one of the most common diseases in industrialized countries. In the United States it accounts for about 1% of all health care costs. An alarming increase in both the prevalence and mortality of asthma over the past decade has been reported, and asthma is predicted to be the preeminent occupational lung disease in the next decade. While the increasing mortality of asthma in industrialized countries could be attributable to the depletion reliance upon beta agonists in the treatment of this disease, the underlying causes of asthma remain poorly understood. Respiratory and pulmonary diseases such as asthma, allergic rhinitis, Acute Respiratory Distress Syndrome (ARDS), including that occurring in pregnant mothers and in premature born infants, pulmonary fibrosis, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and cancer, among others, are common diseases in industrialized countries. In the United States alone they account for extremely high health care costs, and their incidence has recently been increasing at an alarming rate, both in terms of prevalence, morbidity and mortality. In spite of this, their underlying causes still remain poorly understood.

Asthma is a condition characterized by variable, in many instances reversible obstruction of the airways. This process is associated with lung inflammation and in some cases lung allergies. Many patients have acute episodes referred to as "asthma attacks," while others are afflicted with a chronic condition. The asthmatic process is triggered in some cases by inhalation of antigens by hypersensitive subjects. This condition is generally referred to as "extrinsic asthma." Other asthmatics have an intrinsic predisposition to the condition, which is thus referred to as "intrinsic asthma," and may be comprised of conditions of different origin, including those mediated by the adenosine receptor(s), allergic conditions mediated by an immune IgE-mediated response, and others. All asthmas have a group of symptoms, which are characteristic of this condition: bronchoconstriction, lung inflammation and decreased lung surfactant. Existing bronchodilators and anti-inflammatories are currently commercially available and are prescribed for the treatment of asthma. The most common anti-inflammatories, corticosteroids, have considerable side effects but are commonly prescribed nevertheless. Most of the drugs available for the treatment of asthma are, more importantly, barely effective in a small number of patients.

Acute Respiratory Distress Syndrome (ARDS), or stiff lung, shock lung, pump lung and congestive atelectasis, is believed to be caused by fluid accumulation within the lung which, in turn, causes the lung to stiffen. The condition is triggered within 48 hours by a variety of processes that injure the lungs such as trauma, head injury, shock, sepsis, multiple blood transfusions, medications, pulmonary embolism, severe pneumonia, smoke inhalation, radiation, high altitude, near drowning, and others. In general, ARDS occurs as a medical emergency and may be caused by other conditions that directly or indirectly cause the blood vessels to "leak" fluid into the lungs. In ARDS, the ability of the lungs to expand is severely decreased and produces extensive damage to the air sacs and lining or endothelium of the lung. ARDS' most common symptoms are labored, rapid breathing, nasal flaring,



5 cyanosis blue skin, lips and nails caused by lack of oxygen to the tissues, breathing difficulty, anxiety, stress, tension, joint stiffness, pain and temporarily absent breathing. ARDS is commonly diagnosed by testing for symptomatic signs, for example by a simple chest auscultation or examination with a stethoscope that may reveal abnormal symptomatic breath sounds. A preliminary diagnosis of ARDS may be confirmed with chest X-rays and the measurement of arterial blood gas. In some cases ARDS appears to be associated with other diseases, such as acute myelogenous leukemia, with acute tumor lysis syndrome (ATLS) developed after treatment with, e.g. cytosine arabinoside. In general, however, ARDS appears to be associated with traumatic injury, severe blood infections such as sepsis, or other systemic illness, high dose radiation therapy and chemotherapy, and inflammatory responses which lead to multiple organ failure, and in many cases death. In premature babies ("premies"), the lungs are not quite developed and, therefore, the fetus is in an anoxic state during development. Moreover, lung surfactant, a material critical for normal respiration, is generally not yet present in sufficient amounts at this early stage of life; however, premies often hyper-express the adenosine A<sub>1</sub> receptor and/or underexpress the adenosine A<sub>2A</sub> receptor and are, therefore, susceptible to respiratory problems including bronchoconstriction, lung inflammation and ARDS, among others. When Respiratory Distress Syndrome (RDS) occurs in premies, it is an extremely serious problem. 15 Preterm infants exhibiting RDS are currently treated by ventilation and administration of oxygen and surfactant preparations. When premies survive RDS, they frequently develop bronchopulmonary dysplasia (BPD), also called chronic lung disease of early infancy, which is often fatal.

The systemic administration of adenosine was found useful for treating SVT, and as a pharmacologic means to evaluate cardiovascular health via an adenosine stress test commonly administered by hospitals and by doctors in private practice. Adenosine administered by inhalation, however, is known to cause bronchoconstriction in asthmatics, possibly due to mast cell degranulation and histamine release, effects which have not been observed in normal subjects. Adenosine infusion has caused respiratory compromise, for example, in patients with COPD. As a consequence of the untoward side effects observed in many patients, caution is recommended in the prescription of adenosine to patients with a variety of conditions, including obstructive lung disease, emphysema, bronchitis, etc, and complete avoidance of its administration to patients with or prone to bronchoconstriction or bronchospasm, such as asthma. In addition, the administration of adenosine must be discontinued in any patient who develops severe respiratory difficulties. It would be of great help if a formulation were to be made available for joint use when adenosine administration is required. 20

Allergic rhinitis afflicts one in five Americans, accounting for an estimated \$4 to 10 billion in health care costs each year, and occurs at all ages. Because many people mislabel their symptoms as persistent colds or sinus problems, allergic rhinitis is probably underdiagnosed. Typically, IgE combines with allergens in the nose to produce chemical mediators, induction of cellular processes, and neurogenic stimulation, causing an underlying inflammation. Symptoms include nasal congestion, discharge, sneezing, and itching, as well as itchy, watery, swollen eyes. Over time, allergic rhinitis sufferers often develop sinusitis, otitis media with effusion, and nasal polyposis that may exacerbate asthma, and is associated with mood and cognitive disturbances, fatigue and irritability. Degranulation of mast cells results in the release of preformed mediators that interact with various cells, blood vessels, and mucous glands to produce the typical rhinitis symptoms. Most early- and late-phase reactions occur in the nose after allergen exposure. The late-phase reaction is seen in chronic allergic rhinitis, with hypersecretion and congestion as the most prominent symptoms. Repeated exposure may cause hypersensitivity to one or many allergens. Sufferers may also become hyperreactive to non-specific triggers, such as cold air or strong odors. Non-allergic rhinitis may be induced by infections, such as viral infections, or associated with nasal polyps, as occurs in patients with aspirin idiosyncrasy. In addition, pregnancy, hypothyroidism, and exposure to occupational factors or medications may cause rhinitis, as well. NARES syndrome, a non-allergic type of rhinitis associated with eosinophils in nasal secretions, typically occurs in middle-aged individuals and is accompanied by loss of smell. Saline is often recommended to improve nasal stuffiness, sneezing, and congestion, since saline sprays usually relieve mucosal irritation or dryness associated with various nasal conditions, minimize mucosal atrophy, and dislodge encrusted or thickened mucus, while causing no side effects, and may be used freely in pregnant patients. In addition, if used immediately before intra-nasal corticosteroid dosing, saline helps prevent local irritation. Anti-histamines often serve as a primary therapy. Terfenadine and astemizole, two non-sedating anti-histamines, however, have been associated with a ventricular arrhythmia known as Torsades de Points, usually in interaction with other medications such as ketoconazole and erythromycin, or secondary to an underlying cardiac problem. Up to date, loratadine, another nonsedating anti-histamine, and cetirizine have not been associated with 25 30 35 40 45 50

serious adverse cardiovascular events. Cetirizine's most common side effect, however, is drowsiness. Claritin, for example, may be effective in relieving sneezing, runny nose, and nasal, ocular and palatal itching in a low percentage of patients, although not approved for this indication or asthma. Anti-histamines are typically combined with a decongestant to help relieve nasal congestion. Sympathomimetic medications are used as vasoconstrictors and decongestants, the most common being pseudoephedrine, phenylpropanolamine and phenylephrine. These agents, however, often cause hypertension, palpitations, tachycardia, restlessness, insomnia and headache. Topical decongestants are recommended for limited periods because their overuse results in nasal dilatation. Anti-cholinergic agents, such as cromolyn, have a role in patients with significant rhinorrhea or in specific cases, such as "gustatory rhinitis", which is usually associated with ingestion of spicy foods, and have been used on the common cold. Sometimes the Cromolyn spray produces sneezing, transient headache, and even nasal burning. Topical and nasal spray corticosteroids such as Vancenase are effective agents in the treatment of rhinitis, especially for symptoms of congestion, sneezing and runny nose, but sometimes may cause irritation, stinging, burning, sneezing, and local bleeding. Topical steroids are generally more effective than Cromolyn sodium, particularly in the treatment of NARES, but side effects sometimes limit their usefulness. Immunotherapy, while expensive and inconvenient, often provides substantial benefits, especially the use of drugs such as blocking antibodies, and those that alter cellular histamine release, and result in decreased IgE. Presently available treatments, such as propranolol, verapamil, and adenosine, may help to minimize symptoms. Verapamil is most commonly used but it has several shortcomings, since it causes or exacerbates systemic hypotension, congestive heart failure, bradyarrhythmias, and ventricular fibrillation. Verapamil, however, crosses the placenta and has been shown to cause fetal bradycardia, heart block, depression of contractility, and hypotension. Adenosine has several advantages over verapamil, including rapid onset, brevity of side effects, theoretical safety, and probable lack of placental transfer, but may not be administered to a variety of patients.

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction that is generally caused by chronic bronchitis, emphysema, or both. Emphysema is characterized by abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. Chronic bronchitis is characterized by chronic cough, mucus production, or both, for at least three months for at least two successive years where other causes of chronic cough have been excluded. COPD characteristically affects middle aged and elderly people, and is one of the leading causes of morbidity and mortality worldwide. In the United States it affects about 14 million people and is the fourth leading cause of death, and both its morbidity and mortality rates are still rising. This contrasts with the decline over the same period in age-adjusted mortality from all causes, and from cardiovascular diseases. COPD, however, is preventable, since it is believed that its main cause is exposure to cigarette smoke. The disease is rare in lifetime non-smokers, in whom exposure to environmental tobacco smoke will explain at least some of the airways obstruction. Other proposed etiological factors include airway hyper-responsiveness or hypersensitivity, ambient air pollution, and allergy. The airflow obstruction in COPD is usually progressive in people who continue to smoke. This results in early disability and shortened survival time. Stopping smoking reverts the decline in lung function to values for non-smokers. Many patients will use medication chronically for the rest of their lives, with the need for increased doses and additional drugs during exacerbations. Amongst the currently available treatments for COPD, short-term benefits were found, as opposed to long term effects on progression, from anti-cholinergic drugs,  $\beta_2$  adrenergic agonists, and oral steroids. The effects of anti-cholinergic drugs and  $\beta_2$  adrenergic agonists, however, are not seen in all people with COPD, and the two agents combined are only slightly more effective than either alone. Their adverse effects and the need for frequent monitoring of blood concentrations limit the usefulness of theophyllines. There is no evidence that anti-cholinergic agents affect the decline in lung function, and mucolytics have been shown to reduce the frequency of exacerbations but with a possible deleterious effect on lung function. The long-term effects of  $\beta_2$  adrenergic agonists, oral corticosteroids, and antibiotics have not yet been evaluated, and up to the present time no other drug has been shown to affect the progression of the disease or survival. Thus, there is very little currently available to alleviate symptoms of COPD, prevent exacerbations, preserve optimal lung function, and improve daily living activities an quality of life. Thus, there is very little currently available to alleviate symptoms of COPD, prevent exacerbations, preserve optimal lung function, and improve daily living activities an quality of life.

Interstitial lung disease (ILD), interstitial pulmonary fibrosis, or simply pulmonary fibrosis are terms that include more than 130 chronic lung disorders that affect the lung in at least three ways: lung tissue is damaged in some known or unknown way, walls of the air sacs in the lung become inflamed, and scarring or fibrosis begins in

the interstitium (or tissue between the air sacs), and the lung becomes stiff. Breathlessness during exercise may be one of the first symptoms of these diseases, and a dry cough may be present. Neither the symptoms nor X rays are often sufficient to tell apart different types of pulmonary fibrosis. Some pulmonary fibrosis patients have known causes and some have unknown or idiopathic causes. Interstitial lung disease (or pulmonary fibrosis) is named after  
5 he tissue between the air sacs of the lungs because this is the tissue affected by fibrosis or scarring. The course of this disease is generally unpredictable. If they progress the lung tissue thickens and becomes stiff, breathing becomes more difficult and demanding, and inflammation occurs. Some people may need oxygen therapy as part of their treatment.

Microbial infections are extremely common, and may be caused by viruses, bacteria, and other forms of  
10 life. They are generally treated with anti-viral agents, antibiotics, and other specific therapeutic drugs. However, some infectious may either go unnoticed, or produce secondary effects such as inflammation, pulmonary and airway obstructions, and other pulmonary ailments.

Cancer is one of the most prevalent and feared diseases of our times. It generally results from the carcinogenic transformation of normal cells of different epithelia. Two of the most damaging characteristics of  
15 carcinomas and other types of malignancies are their uncontrolled growth and their ability to create metastases in distant sites of the host, particularly a human host. It is usually these distant metastases that cause serious consequences to the host, since frequently the primary carcinoma may be, in most cases, removed by surgery. The treatment of cancer presently relies on surgery, irradiation therapy and systemic therapies such as chemotherapy, different immunity-boosting medicines and procedures, hyperthermia and systemic, radioactively labeled monoclonal antibody treatment,  
20 immunotoxins and chemotherapeutic drugs.

Adenosine may constitute an important mediator in the lung for various diseases, including bronchial asthma, COPD, CF, RDS, rhinitis, pulmonary fibrosis, and others. Its potential role was suggested by the finding that asthmatics respond favorably to aerosolized adenosine with marked bronchoconstriction whereas normal  
25 individuals do not. An asthmatic rabbit animal model, the dust mite allergic rabbit model for human asthma, responded in a similar fashion to aerosolized adenosine with marked bronchoconstriction whereas non-asthmatic rabbits showed no response. More recent work with this animal model suggested that adenosine-induced bronchoconstriction and bronchial hyperresponsiveness in asthma may be mediated primarily through the stimulation of adenosine receptors. Adenosine has also been shown to cause adverse effects, including death, when administered therapeutically for other diseases and conditions in subjects with previously undiagnosed hyper  
30 reactive airways.

Adenosine is a purine involved in intermediary metabolism, and may constitute an important natural mediator of many of diseases. Adenosine plays a unique role in the body as a regulator of cellular metabolism. It can raise the cellular level of AMP, ADP and ATP which are the energy intermediates of the cell. Adenosine can stimulate or down regulate the activity of adenylate cyclase and hence regulate cAMP levels. cAMP, in turn, plays a  
35 role in neurotransmitter release, cellular division and hormone release. Adenosine's major role appears to be to act as a protective injury autocoid. In any condition in which ischemia, low oxygen tension or trauma occurs adenosine appears to play a role. Defects in synthesis, release, action and/or degradation of adenosine have been postulated to contribute to the over activity of the brain excitatory amino acid neurotransmitters, and hence various pathological states. Adenosine has also been implicated as a primary determinant underlying the symptoms of bronchial asthma  
40 and other respiratory diseases, the induction of bronchoconstriction and the contraction of airway smooth muscle. Moreover, adenosine causes bronchoconstriction in asthmatics but not in non-asthmatics. Other data suggest the possibility that adenosine receptors may also be involved in allergic and inflammatory responses by reducing the hyperactivity of the central dopaminergic system. It has been postulated that the modulation of signal transduction at the surface of inflammatory cells influences acute inflammation. Adenosine is said to inhibit the production of  
45 super-oxide by stimulated neutrophils. Recent evidence suggests that adenosine may also play a protective role in stroke, CNS trauma, epilepsy, ischemic heart disease, coronary by-pass, radiation exposure and inflammation. Overall, adenosine appears to regulate cellular metabolism through ATP, to act as a carrier for methionine, to decrease cellular oxygen demand and to protect cells from ischemic injury. Adenosine is a tissue hormone or inter-cellular messenger that is released when cells are subject to ischemia, hypoxia, cellular stress, and increased  
50 workload, and or when the demand for ATP exceeds its supply. Adenosine is a purine and its formation is directly linked to ATP catabolism. It appears to modulate an array of physiological processes including vascular tone, hormone action, neural function, platelet aggregation and lymphocyte differentiation. It also may play a role in

DNA formation, ATP biosynthesis and general intermediary metabolism. It is suggested that it regulates the formation of cAMP in the brain and in a variety of peripheral tissues. Adenosine regulates cAMP formation through two receptors  $A_1$  and  $A_2$ . Via  $A_1$  receptors, adenosine reduces adenylate cyclase activity, while it stimulates adenylate cyclase at  $A_2$  receptors. The adenosine  $A_1$  receptors are more sensitive to adenosine than the  $A_2$  receptors.

5 The CNS effects of adenosine are generally believed to be  $A_1$ -receptor mediated, where as the peripheral effects such as hypotension, bradycardia, are said to be  $A_2$  receptor mediated.

Anti-sense oligonucleotides have received considerable theoretical consideration as potential useful pharmacological agents in human disease. One important impediment to their effective application has been a difficulty in finding an appropriate route of administration to deliver them to their site of action. The administering

10 of anti-sense oligonucleotides directly to specific regions of the brain, for example, necessarily has limited clinical utility due to its invasive nature. Finding practical and effective applications for these agents in actual models of human disease have been few and far between, particularly because they had to be administered in large doses. The systemic administration of anti-sense oligonucleotides as pharmacological agents, such as oral and parenteral administration, has been found to have also significant problems, including the inherent difficulty in targeting

15 specific tissues due to their dilution in the circulatory system. The bioavailability of orally administered anti-sense oligonucleotides is very low, of the order of less than about 5%. The present inventor previously pioneered the administration of oligonucleotides via the respiratory system, and successfully treated asthma, bronchoconstriction and lung inflammation and allergies, and applied the technology to the treatment of other conditions. The route of administration, thus was found to be of importance, particularly for treating localized conditions. As described in

20 more detail below, the lung is an excellent target for the direct administration of anti-sense oligonucleotides and provides a non-invasive and a tissue-specific route. The respiratory system, and in particular the lung, as the ultimate port of entry into the organism provides an excellent route of administration for anti-sense oligonucleotides. This is so not only for the treatment of lung disease, but also when utilizing the lung as a means for delivery, particularly because of its non-invasive and tissue-specific nature. Thus, local delivery of anti-sense oligos directly

25 to the target tissue enables an optimal delivery for the therapeutic use of these compounds. Fomivirsen (ISIS 2922) is an example of a local drug delivery into the eye to treat cytomegalovirus (CMV) retinitis, for which a new drug application has been filed by ISIS. The administration of a drug through the lung offers the further advantage that inhalation is non-invasive whereas direct injection into the vitreous of the eye is invasive.

Steroids are naturally occurring compounds of varied activities. In mammals, they serve different functions, some being associated with sexual cycles and reproduction, others with regulation of endogenous levels of various compounds. Some of these have anti-inflammatory activity,

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Steroid hormones are potent chemical messengers that exert dramatic effects on cell differentiation, homeostasis, and morphogenesis. These molecules diverse in structure share a mechanistically similar mode of action. The effector molecules diffuse across cellular membranes and bind to specific high affinity receptors in the

35 target cell nuclei. This interaction results in the conversion of an inactive receptor to one that can interact with the regulatory regions of target genes and modulate the rate of transcription of specific gene sets. Upon ligand binding, these receptors generate both rapid and long lasting responses. Steroids can act through two basic mechanisms: genomic and non-genomic. The classical genomic action is mediated by specific intracellular receptors, whereas the primary target for the non-genomic one is the cell membrane. Many clinical symptoms seem to be mediated

40 through the non-genomic route. Furthermore, membrane effects of steroid and other factors can interfere with the intranuclear receptor system inducing or repressing steroid- and receptor-specific genomic effects. These signalling pathways may lead to unexpected hormonal or anti-hormonal effects in patients treated with certain drugs.

Steroid receptors are members of a large family of nuclear transcription factors that regulate gene expression by binding to their cognate steroid ligands, to the specific enhancer sequences of DNA (steroid response

45 elements) and to the basic transcription machinery. Steroid receptors are basically localized in the nucleus, regardless of hormonal status, and considerable-amounts of unliganded steroid receptors may be present in the cytoplasm of target cells in exceptional cases. Most steroid receptors are phosphoproteins, which are further phosphorylated after ligand binding. The role of phosphorylation in receptor transaction is complex and may not be uniform to all steroid receptors. However, phosphorylation and/or dephosphorylation is believed to be a key event

50 regulating the transcriptional activity of steroid receptors. Steroid receptor activities can be affected by the amount of steroid receptor in the cell nuclei, which is modified by the rate of transcription and translation of the steroid receptor gene as well as by proteolysis of the steroid receptor protein. There is an auto- and heteroregulation of

receptor levels. Some of the steroid receptors appear to bind specific protease inhibitors and exhibit protease activity. Some steroid receptors are expressed as two or more isoforms, which may have different effects on transcription. Receptor isoforms are different translation or transcription products of a single gene. Isoform A of the progesterone receptor is a truncated form of PR isoform B originating from the same gene, but it is able to suppress not only the gene enhancing activity of PR-B but also that of other steroid receptors.

Before hormone binding, the receptors are part of a complex with multiple chaperones which maintain the receptor in its steroid binding conformation. Following hormone binding, the complex dissociates and the receptors bind to steroid response elements in chromatin. Regulation of gene expression by hormones involves an interaction of the DNA-bound receptors with other sequence-specific transcription factors and with the general transcription factors, which is partly mediated by co-activators and co-repressors. The specific array of cis regulatory elements in a particular promoter/enhancer region, as well as the organization of the DNA sequences in nucleosomes, specifies the network of receptor interactions. Depending on the nature of these interactions, the final outcome can be induction or repression of transcription.

Adrenocortical hormones are steroid hormones classified as glucocorticoids, mineralocorticoids and sex hormones. Glucocorticoids moderate the metabolism of sugar, fat and protein and may raise the resistance to the adverse stimulation of the body by these substances. Many of the clinically useful steroids belong to this group, including cortisone, hydrocortisone, and their pharmaceutical derivatives such as prednisone, dexamethasone, etc. Although glucocorticoids were originally so called because of their influence on glucose metabolism, they are currently defined as steroids that exert their effects by binding to specific cytosolic receptors that mediate the actions of these hormones. These glucocorticoid receptors are present in virtually all tissues, and glucocorticoid-receptor interactions are responsible for most of the known effects of these steroids. Alteration in the structure of these glucocorticoids has led to the development of synthetic compounds with greater glucocorticoid activity. The increased activity of these compounds is due to increased affinity for the glucocorticoid receptors and/or delayed plasma clearance, which increases tissue exposure. In addition, many of these synthetic glucocorticoids evidence negligible mineralocorticoid effects and thus do not result in sodium retention, hypertension, and/or hypokalemia. Glucocorticoid action is initiated by entry of the steroid into the cell and binding to the cytosolic glucocorticoid receptor proteins. After binding, activated hormone-receptor complexes enter the nucleus and interact with nuclear chromatin acceptor sites. These events cause the expression of specific genes and the transcription of specific mRNAs. The resulting proteins affect the response to the glucocorticoids, which may be inhibitory or stimulatory depending on the specific tissue affected. Although glucocorticoid receptors are similar in many tissues, the proteins synthesized vary widely and are the result of expression of specific genes in different cell types.

Mineralocorticoids and sex hormones are non-glucocorticoid steroids, e.g., adrenal androgens. Adrenal androgens, such as androstenediones, dehydroepiandrosterone (DHEA), and DHEA sulfate function as precursors for the peripheral conversion to androgenic hormones, such as testosterone and dihydrotestosterone. DHEA sulfate secreted by the adrenal undergoes limited conversion to DHEA, and both the peripheral DHEA and DHEA secreted by the adrenal cortex may be further converted in peripheral tissues to androstenedione, the immediate precursor of the active androgens. Dehydroepiandrosterone (DHEA) is a naturally occurring steroid secreted by the adrenal cortex with apparent chemoprotective properties. Epidemiological studies have shown that low endogenous levels of DHEA correlate with increased risk of developing some forms of cancer, such as pre-menopausal breast cancer in women and bladder cancer in both sexes. The ability of DHEA and DHEA analogues, e.g. dehydroepiandrosterone sulfate (DHEA-S), to inhibit carcinogenesis is believed to result from their uncompetitive inhibition of the activity of the enzyme glucose 6-phosphate dehydrogenase (G6PDH). G6PDH is the rate limiting enzyme of the hexose monophosphate pathway, a major source of intracellular ribose-5-phosphate and NADPH. Ribose-5 phosphate is a necessary substrate for the synthesis of both ribo- and deoxyribonucleotides required for the synthesis of RNA and DNA. NADPH is a cofactor also involved in nucleic acid biosynthesis and the synthesis of hydroxymethylglutaryl Coenzyme A reductase (HMG CoA reductase). HMG CoA reductase is an unusual enzyme that requires two moles of NADPH for each mole of product, mevalonate, produced. Thus, it appears that HMG CoA reductase would be ultrasensitive to DHEA-mediated NADPH depletion, and that DHEA-treated cells would rapidly show the depletion of intracellular pools of mevalonate. Mevalonate is required for DNA synthesis, and DHEA arrests human cells in the G1 phase of the cell cycle in a manner closely resembling that of the direct HMG CoA. Because G6PDH produces mevalonic acid used in cellular processes such as protein isoprenylation and the synthesis of dolichol, a precursor for glycoprotein biosynthesis, DHEA inhibits carcinogenesis by depleting mevalonic acid and thereby

inhibiting protein isoprenylation and glycoprotein synthesis. Mevalonate is a central precursor for the synthesis of cholesterol, as well as for the synthesis of a variety of non-sterol compounds involved in post-translational modification of proteins, such as farnesyl pyrophosphate and geranyl pyrophosphate. Mevalonate is also a central precursor for the synthesis of dolichol, a compound that is required for the synthesis of glycoproteins involved in cell-to-cell communication and cell structure. Mevalonate is also central to the manufacture of ubiquinone, an antioxidant with an established role in cellular respiration. It has long been known that patients receiving steroid hormones of adrenocortical origin at pharmacologically appropriate doses show increased incidence of infectious disease.

DHEA, also known as  $3\beta$ -hydroxyandrost-5-en-17-one or dehydroepiandrosterone, is a 17-ketosteroid which is quantitatively one of the major adrenocortical steroid hormones found in mammals. Although DHEA appears to serve as an intermediary in gonadal steroid synthesis, the primary physiological function of DHEA has not been fully understood. It has been known, however, that levels of this hormone begin to decline in the second decade of life, reaching 5% of the original level in the elderly.) Clinically, DHEA has been used systemically and/or topically for treating patients suffering from psoriasis, gout, hyperlipemia, and it has been administered to post-coronary patients. In mammals, DHEA has been shown to have weight optimizing and anti-carcinogenic effects, and it has been used clinically in Europe in conjunction with estrogen as an agent to reverse menopausal symptoms and also has been used in the treatment of manic depression, schizophrenia, and Alzheimer's disease. DHEA has also been used clinically at 40 mg/kg/day in the treatment of advanced cancer and multiple sclerosis. Mild androgenic effects, hirsutism, and increased libido were the side effects observed. These side effects can be overcome by monitoring the dose and/or by using analogues. The subcutaneous or oral administration of DHEA to improve the host's response to infections is known, as is the use of a patch to deliver DHEA. DHEA is also known as a precursor in a metabolic pathway that ultimately leads to more powerful agents that increase immune response in mammals. That is, DHEA acts as a biphasic compound: it acts as an immuno-modulator when converted to androstenediol or androst-5-ene- $3\beta$ ,17 $\beta$ -diol ( $\beta$ AED), or androstenediol or androst-5-ene- $3\beta$ ,7 $\beta$ ,17 $\beta$ -triol ( $\beta$ AET). However, in vitro DHEA has certain lymphotoxic and suppressive effects on cell proliferation prior to its conversion to  $\beta$ AED and/or  $\beta$ AET. It is, therefore, believed that the superior immunity enhancing properties obtained by administration of DHEA result from its conversion to more active metabolites.

Adequate ubiquinone levels have been found to be essential for maintaining proper cardiac function, and the administration of exogenous ubiquinone has recently been shown to have beneficial effect in patients with chronic heart failure. Ubiquinone depletion has been observed in humans and animals treated with lovastatin, a direct HMG CoA reductase inhibitor. Such lovastatin-induced depletion of ubiquinone has been shown to lead to chronic heart failure, or to a shift from low heart failure into life-threatening high grade heart failure. DHEA, unlike lovastatin, inhibits HMG CoA reductase indirectly by inhibiting G6PDH and depleting NADPH, a required cofactor for HMG CoA reductase. However, DHEA's indirect inhibition of HMG CoA reductase suffices to deplete intracellular mevalonate. This effect adds to the depletion of ubiquinone, and may result in chronic heart failure following long term usage. Thus, although DHEA was once considered a safe drug, it is now predicted that with long term administration of DHEA or its analogues, chronic heart failure may occur as a complicating side effect. Further, some analogues of DHEA produce this side effect to a greater extent because, in general, they are more potent inhibitors of G6PDH than DHEA.

A handful of medicaments have been used for the treatment of respiratory diseases and conditions, although in general they all have limitations. Amongst them are corticoid steroids with glucocorticoid activity, leukotriene inhibitors, anti-cholinergic agents, anti-histamines, oxygen therapy, theophyllines, and mucolytics. Corticosteroids are the ones with the most widespread use in spite of their well documented side effects. Most of the available drugs are nevertheless effective in a small number of cases, and not at all when it comes to the treatment of asthma. No treatments are currently available for many of the other respiratory diseases. Theophylline, an important drug in the treatment of asthma, is a known adenosine receptor antagonist that was reported to eliminate adenosine-mediated bronchoconstriction in asthmatic rabbits. A selective adenosine  $A_1$  receptor antagonist, 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX) was also reported to inhibit adenosine-mediated bronchoconstriction and bronchial hyperresponsiveness in allergic rabbits. The therapeutic and preventative applications of currently available adenosine  $A_1$  receptor-specific antagonists are, nevertheless, limited by their toxicity. Theophylline, for example, has been widely used in the treatment of asthma, but is associated with frequent, significant toxicity resulting from its narrow therapeutic dose range. DPCPX is far too toxic to be useful clinically. The fact that, despite decades of

extensive research, no specific adenosine receptor antagonist is available for clinical use attests to the general toxicity of these agents.

For many years, two classes of compounds have dominated the treatment of asthma: corticosteroids having glucocorticoid activity and bronchodilators. Examples of corticosteroids are beclomethasone and corticoid 21-sulfopropionates. Examples of a bronchodilator are an older  $\beta_2$  adrenergic agonist such as albuterol, and a newer one such as salmeterol. In general, when glucocorticosteroids are taken daily either by inhalation or orally, they attenuate inflammation. The  $\beta_2$  adrenergic agonists, on the other hand, primarily alleviate bronchoconstriction. Whereas glucocorticosteroids are not useful in general for acute settings, bronchodilators are used in acute care, such as in the case of asthma attacks. At the present time, many asthma patients require daily use of both types of agents, a glucocorticosteroid to contain pulmonary inflammation, and a bronchodilator to alleviate bronchoconstriction. More recently, fluticasone propionate, a corticosteroid was combined with  $\beta_2$  adrenergic agonists in one therapeutic formulation said to have greater efficiency in the treatment of asthma. However, glucocorticosteroids, particularly when taken for prolonged periods, have extremely deleterious side effects that, although somewhat effective, make their chronic use undesirable, particularly in children.

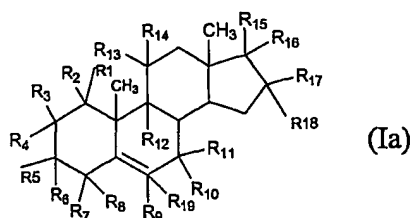
Clearly, there exists a well defined need for novel and effective therapies for treating respiratory, lung and cancer ailments that cannot presently be reasonably treated, or at least for which no therapies are available that are effective and devoid of significant detrimental side effects. Moreover, there is a definite need for treatments that have prophylactic and therapeutic applications, and require low amounts of active agents, and are less costly and less prone to detrimental side effects. Furthermore, it is readily apparent that anti-inflammatory steroids ("AIS"), including adrenal androgens, androgens and their derivatives, etc, corticoid and non-glucocorticoid steroids, ubiquinones and their respective salts, as well as specifically targeted anti-sense oligonucleotides (oligos) are each alone useful for the treatment of respiratory, lung, and cancer. This patent provides their joint effects that evidence unexpected superior results over each agent alone.

## SUMMARY OF THE INVENTION

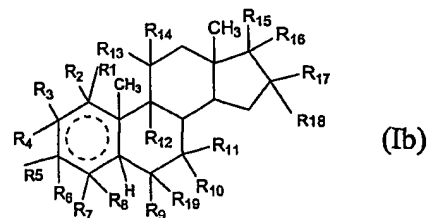
The present invention generally relates to a pharmaceutical or veterinary composition, comprising a pharmaceutically or veterinarily acceptable carrier or diluent, and first and second active agents.

The first active agent comprises an oligonucleotide(s) (oligo(s)) that may be anti-sense to one or more targets, and a second active agent comprising anti-inflammatory steroids ("AIS") and/or a ubiquinone, in amounts effective for alleviating airway, lung, and microbial and/or cancer diseases associated with, for example, bronchoconstriction, impeded respiration, dyspnea, emphysema, asthma, COPD, ARDS, CF, allergic rhinitis, pulmonary hypertension and fibrosis, lung inflammation, allergies, surfactant depletion or hyposecretion, and cancers, among others. The oligo preferably contains about 0 to about 15% adenosine (A) and is anti-sense to the initiation codon, the coding region, the 5'-end or the 3'-end genomic flanking regions, the 5' or 3' intron-exon junctions, or regions within 2 to 10 nucleotides of the junctions of at least one gene regulating or encoding a target polypeptide associated with lung or airway dysfunction or cancer, or that is anti-sense to the corresponding mRNA, and the composition may comprise also combinations or mixtures of the oligos. The targets are typically molecules associated with airway disease, cancer, etc., such as transcription factors, stimulating and activating peptide factors, cytokines, cytokine receptors, chemokines, chemokine receptors, adenosine receptors, bradykinin receptors, endogenously produced specific and non-specific enzymes, immunoglobulins and antibodies, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensins, growth factors, vasoactive peptides and receptors, binding proteins, and malignancy associated proteins, among others. In one embodiment the first active agent comprises a nucleic acid wherein the oligo is anti-sense to more than one target. These are called within the four corners of this patent multiple target anti-sense oligonucleotides or MTAs.

The second active agent comprises an anti-inflammatory steroid such as an adrenal androgen of the chemical formula



or

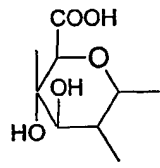


wherein  $R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9, R_{10}, R_{12}, R_{13}, R_{14}$  and  $R_{19}$  are independently H, OR, halogen,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene,  $(C_1-C_{10})$  alkyne,  $(C_1-C_{10})$  alkoxy, or two or more of  $R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9, R_{10}, R_{12}, R_{13}, R_{14}$  and  $R_{19}$  can be linked by combination of the atoms of C, O, N, S, P and Si to form a 3 to 15 member ring(s), in the  $\alpha$ - and/or  $\beta$ - configuration;

$R_5, R_6, R_{10}$ , and  $R_{11}$  are independently OH, SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane,  $-OSO_2R_{20}$ ,  $-OPOR_{20}R_{21}$ ,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene,  $(C_1-C_{10})$  alkyne or  $OR_{23}$ ,  $-SO_2O-CH_2CHCH_2OCOR_{25}$

wherein,  $R_{23}$  is hydrogen or  $SO_2OM$ , wherein M is selected from H, Na, sulfatide;

$-PO_2O-CH_2CHCH_2OCOR_{25}$   
phosphatide  $OCOR_{24}$ , wherein  $R_{24}$  and  $R_{25}$ , which may be the same or different, are straight or branched  $(C_1-C_{20})$  alkyl,  $(C_1-C_{20})$  alkene,  $(C_1-C_{20})$  alkyne, sugar, polyethyleneglycol (PEG) or glucuronide



$R_5$  and  $R_6$  taken together are  $=O$ ;  
 $R_{10}$  and  $R_{11}$  taken together are  $=O$ ;

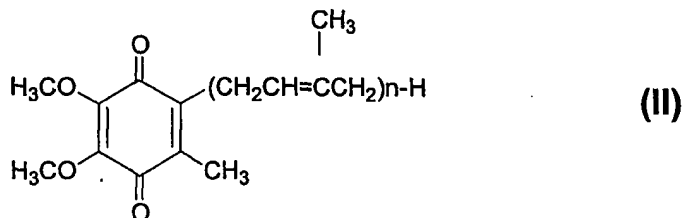
$R_{15}$  is (1) H, halogen,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene,  $(C_1-C_{10})$  alkyne, or  $(C_1-C_{10})$  alkoxy when  $R_{16}$  is  $-C(O)OR_{22}$ , (2) H, halogen, OH,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene or  $(C_1-C_{10})$  alkyne, when  $R_{16}$  is halogen, OH,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene or  $(C_1-C_{10})$  alkyne, (3) H, halogen,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkenyl,  $(C_1-C_{10})$  alkynyl, formyl,  $(C_1-C_{10})$  alkanoyl or epoxy when  $R_{16}$  is OH, (4) OR, SR, SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane,  $-OSO_2R_{20}$  or  $-OPOR_{20}R_{21}$  when  $R_{16}$  is H, or  $R_{15}$  and  $R_{16}$  taken together are  $=O$ ;

$R_{17}$  and  $R_{18}$  are independently (1) H,  $-OH$ , halogen,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene,  $(C_1-C_{10})$  alkyne or  $-(C_1-C_{10})$  alkoxy when  $R_5$  is H OR, halogen,  $(C_1-C_{10})$  alkyl or  $-C(O)OR_{22}$ , (2) H,  $(C_1-C_{10})$  alkyl<sub>n</sub> amino,  $(C_1-C_{10})$  alkene<sub>n</sub> amino,  $(C_1-C_{10})$  alkyne<sub>n</sub> amino,  $((C_1-C_{10})$  alkyl)<sub>n</sub> amino- $(C_1-C_{10})$  alkyl,  $((C_1-C_{10})$  alkene)<sub>n</sub> amino- $(C_1-C_{10})$  alkyl,  $((C_1-C_{10})$  alkyne)<sub>n</sub> amino- $(C_1-C_{10})$  alkyl,  $((C_1-C_{10})$  alkyl)<sub>n</sub> amino- $(C_1-C_{10})$  alkene,  $((C_1-C_{10})$  alkene)<sub>n</sub> amino- $(C_1-C_{10})$  alkene,  $((C_1-C_{10})$  alkyne)<sub>n</sub> amino- $(C_1-C_{10})$  alkene,  $((C_1-C_{10})$  alkyl)<sub>n</sub> amino- $(C_1-C_{10})$  alkyne,  $((C_1-C_{10})$  alkene)<sub>n</sub> amino- $(C_1-C_{10})$  alkyne,  $((C_1-C_{10})$  alkyne)<sub>n</sub> amino- $(C_1-C_{10})$  alkyne,  $(C_1-C_{10})$  alkoxy, hydroxy -  $(C_1-C_{10})$  alkyl, hydroxy -  $(C_1-C_{10})$  alkene, hydroxy -  $(C_1-C_{10})$  alkyne,  $(C_1-C_{10})$  alkoxy -  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkoxy -  $(C_1-C_{10})$  alkene,  $(C_1-C_{10})$  alkoxy -  $(C_1-C_{10})$  alkyne,  $(halogen)_m$   $(C_1-C_{10})$  alkyl,  $(halogen)_m$   $(C_1-C_{10})$  alkene,  $(halogen)_m$   $(C_1-C_{10})$  alkyne,  $(C_1-C_{10})$  alkanoyl, formyl,  $(C_1-C_{10})$  carbalkoxy or  $(C_1-C_{10})$  alkanoyloxy when  $R_{15}$  and  $R_{16}$  taken together are  $=O$ , (3)  $R_{17}$  and  $R_{18}$  taken together are  $=O$ ; (4)  $R_{17}$  and  $R_{18}$  taken together with the carbon to which they are attached form a 3-6 member ring containing 0 or 1 oxygen atom; or (5)  $R_{15}$  and  $R_{17}$  taken together with the carbons to which they are



attached form an epoxide ring;  $R_{20}$  and  $R_{21}$  are independently OH, pharmaceutically acceptable ester or pharmaceutically acceptable ether;  $R_{22}$  is H, (halogen)<sub>m</sub> (C<sub>1</sub>-C<sub>10</sub>) alkyl, (halogen)<sub>m</sub> (C<sub>1</sub>-C<sub>10</sub>) alkene, (halogen)<sub>m</sub> (C<sub>1</sub>-C<sub>10</sub>) alkyne, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>) alkene or (C<sub>1</sub>-C<sub>10</sub>) alkyne; n is 0, 1 or 2; and m is 1, 2 or 3,

- 5 or pharmaceutically or veterinarily acceptable salts thereof; and/or  
a ubiquinone of the chemical formula



(CoQ<sub>n</sub>);

- 10 wherein n=1 to 12, the agent being present in an amount effective for treating respiratory lung diseases and conditions, or for reducing levels of, or sensitivity to, adenosine or for increasing surfactant or ubiquinone levels in a subject's tissue (s), or pharmaceutically acceptable salts thereof.

- The oligos and the anti-inflammatory steroids ("AIS") and/or ubiquinones (the second agent) are provided in the form of separate compositions and formulations together with a carrier or diluent, and optionally with other therapeutic agents and formulation additives. The first and second active agents are also provided as a single composition in combination with a carrier and other ingredients known in the art, and may be provided jointly or separately contained in a capsule or cartridge, and in the form of a kit. The drawings accompanying this patent form part of the disclosure of the invention, and further illustrate some aspects of the present invention as discussed below.

## 20 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the inhibition of HT-29 SF cells by DHEA.

Figures 2A and 2B illustrate the effects of different amounts of DHEA on cell cycle distribution in HT-29 SF cells.

- Figures 3A and 3B illustrate the reversal of DHEA-induced growth inhibition in HT-29 cells treated with CON: Control; MVA: Mevalonic Acid; SQ: Squaline; CH: Cholesterol; DN: Deoxyribonucleosides; RN: Ribonucleosides.

Figures 4A, 4B, 4C and 4D illustrate the reversal of DHEA-induced G1 arrest in HT-29 SF cells for different durations of treatment with DHEA.

- The invention will now be described in general in conceptual and experimental terms, with reference to specific examples. Other objects, advantages and features of the present invention will become apparent to those skilled in the art from the description that follows.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

- This invention arose from a desire by the inventor to improve on his own prior treatments and those of others for diseases of the respiratory and pulmonary tracts, as well as those that develop elsewhere in the mammalian body. While he previously provided a pioneering treatment for respiratory tract conditions employing oligonucleotide anti-sense to pre-selected targets, and a treatment for respiratory conditions employing dehydroepiandrosterones and ubiquinone, he reasoned further that their combination might produce unexpectedly superior results given their independent mechanisms. Moreover, he posited that the combination of low dose anti-sense oligonucleotide (oligo) therapy with steroids in general and/or ubiquinone therapy would afford the advantage of their independent lack of detrimental side effects when compared with other agents such as steroids alone, and many others that are generally fraught with detrimental side effects and by the need of administering high doses of therapeutic agents. The inventor's prior discovery that variously targeted anti-sense oligonucleotides (oligos) may be utilized therapeutically in the treatment of diseases or conditions which impair respiration, cause inflammation and/or allergy(ies) in the lung and elsewhere, constrict bronchial tissue, obstruct lung airways, deplete surfactant

secretion, and/or otherwise impede normal breathing, lead him to expand his work to their combination with steroids of broad classifications, whose association, either known or discovered by him, with respiratory and pulmonary diseases as well as heart, brain, kidney, skin and other conditions, e.g. ailments associated with hypoxia, infantile Respiratory Disorder Syndrome (RDS), Acute Respiratory Disorder Syndrome (ARDS), aging, cardiac disease, cardiovascular problems, asthma, respiratory distress syndrome, rhinitis, pain, cystic fibrosis (CF), pulmonary hypertension, pulmonary vasoconstriction, pulmonary fibrosis, emphysema, chronic obstructive pulmonary disease (COPD), allergic rhinitis, and cancers such as lung cancer, leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast, liver and prostate cancer, would clearly find an immediate therapeutic application. In general, many diseases and conditions are associated with or cause inflammation, constricted bronchial tissue or lung airways, depletion of surfactant secretion, or augmented respiratory tract allergy(ies), or otherwise impede normal breathing.

The present treatment employs two agents, the first agent being selective for specific targets associated with or mediating these symptoms, and when administered into the airways it is employed in doses up to 1000-fold lower than previously seen in the art. The other agent includes a steroid agent and/or a ubiquinone and provides a more generalized amelioration of the symptoms, also in the substantial absence of undesirable side effects. This treatment further improves on the inventor's prior separate oligonucleotide (oligo) treatment by selecting oligos of reduced adenosine content, or otherwise reducing their adenosine content to reduce the release of free adenosine (A) by breakdown of A-containing oligonucleotides (oligos), thereby avoiding activating adenosine receptors that aggravate bronchoconstriction, and respiratory tract inflammation and allergies, lung surfactant depletion, and the like. As further described below, this patent also provides for the substitution of other bases with a universal base(s) (U) when some characteristic is to be modified. This patent provides novel and improved compositions, formulations, kits and methods which afford greatly improved results when compared with previously known independent treatments for preventing and alleviating bronchoconstriction, allergy(ies), inflammation, breathing difficulties, surfactant depletion and blockage of airways, as well as for preventing and alleviating other conditions and diseases which, directly or indirectly, affect the lung tissue. In different embodiments, one or more nucleic acids of the invention may be formulated for their administration alone or in combination with the steroid agents and/or ubiquinones, surfactant(s), a carrier, and/or other therapeutic agents and formulation agents known in the art. Similarly, the anti-inflammatory steroids and the ubiquinones may be formulated separately for separate administration, or with various formulation components, other therapeutic agents, and the like. By means of example, the steroids and ubiquinone may be administered once or twice daily whereas the oligo may only need be administered once weekly or biweekly.

The single or multiple active agent compositions of this invention are provided in a variety of systemic and topical formulations suitable for the delivery of anti-sense oligonucleotides (oligos) and anti-inflammatory steroids and/or ubiquinones by different routes as a fast means of starting treatment to address asthma and other pulmonary and respiratory tract diseases that may have a rapid onset, where a very low drug dosage is desirable. On the other hand, the oligos have long half-lives and may be administered as preventative of acute episodes, to significantly reduce emergency visits to a doctor or hospital, and as prophylactic maintenance treatment due to the high tolerability of the active agents for prolonged periods of time. In one embodiment, the present treatment provides a once-a-week oligo therapy, accompanied by daily administration of ubiquinone and/or a steroid incorporated into a subject's daily routine. This regime may be effectively administered preventatively, prophylactically and therapeutically, in conjunction with other therapies, or by itself for conditions without known therapies or as a substitute for therapies that have significant negative side effects is also of immediate clinical application. The present treatment also finds an application in the treatment of malignancies, given that steroids and ubiquinones are known for their carcinogenic activities as well as beneficial respiratory effects.

In these cases, the oligo are targeted to cancer-associated nucleic acids and their products. General examples of oligo(s) of the invention are those targeted to a receptor(s) and it (they) are typically present in the composition in an amount effective to reduce that receptor(s) mediated effect(s), and for reducing airway obstruction, lung inflammation and allergy(ies), and surfactant depletion, among others. In one embodiment the receptor is preferably an adenosine receptor such as the adenosine A<sub>1</sub>, A<sub>2b</sub>, or A<sub>3</sub> receptors, and in some instances even adenosine A<sub>2a</sub> receptors. The oligo of the invention may be applied to the preparation of a medicament for reducing bronchoconstriction, impeded respiration, lung inflammation and allergy(ies), depletion of surfactant or

ubiquinone, and for treating respiratory and pulmonary conditions in general, and specific ones such as asthma, ARDS, pulmonary fibrosis, cystic fibrosis, allergic rhinitis, COPD, etc. Many of the conditions targeted by the present treatment afflict a large segment of the population, and either remain unaddressed in terms of therapy or the existing treatments, although heavily advertised, are only mildly effective in small numbers of the afflicted population.

ARDS' most common symptoms are labored, rapid breathing, nasal flaring, cyanosis blue skin, lips and nails caused by lack of oxygen to the tissues, breathing difficulty, anxiety, stress, tension, joint stiffness, pain and temporarily absent breathing. In the following paragraphs, the specific conditions will be described, and the existing treatments, if any, discussed. ARDS is currently diagnosed by mere symptomatic signs, e. g. chest auscultation with a stethoscope that may reveal abnormal symptomatic breath sounds, and confirmed with chest X-rays and the measurement of arterial blood gas. ARDS, in some instances, appears to be associated with other diseases, such as acute myelogenous leukemia, acute tumor lysis syndrome (ATLS) developed after treatment with, e.g. cytosine arabinoside, etc. In general, however, ARDS is associated with traumatic injury, severe blood infections such as sepsis or other systemic illness, high-dose radiation therapy and chemotherapy, and inflammatory responses which lead to multiple organ failure and in many cases death. In premature babies ("premies"), the lungs are not quite developed and, therefore, the fetus is in an anoxic state during development. Moreover, lung surfactant, a material critical for normal respiration, is generally not yet present in sufficient amounts at this early stage of life; however, premies often hyper-express the adenosine A<sub>1</sub> receptor and/or underexpress the adenosine A<sub>2A</sub> receptor and are, therefore, susceptible to respiratory problems including bronchoconstriction, lung inflammation and ARDS, among others. When Respiratory Distress Syndrome (RDS) occurs in premies, it is an extremely serious problem. Preterm infants exhibiting RDS are currently treated by ventilation and administration of oxygen and surfactant preparations. When premies survive RDS, they frequently develop bronchopulmonary dysplasia (BPD), also called chronic lung disease of early infancy, which is often fatal.

Rhinitis may be seasonal or perennial, allergic or non-allergic. Non-allergic rhinitis may be induced by infections, such as viruses, or associated with nasal polyps, as occurs in patients with aspirin idiosyncrasy. Medical conditions such as pregnancy or hypothyroidism and exposure to occupational factors or medications may cause rhinitis. The so-called NARES syndrome is a non-allergic type of rhinitis associated with eosinophils in the nasal secretions, which typically occurs in middle-age and is accompanied by some loss of sense of smell. When cholinergic pathways are stimulated they produce typical secretions that are identified by their glandular constituents so as to implicate neurologic stimulation. Other secretions typical of increased vascular permeability are found in allergic reactions as well as upper respiratory infections, and the degranulation of mast cells releases preformed mediators that interact with various cells, blood vessels, and mucous glands, to produce the typical rhinitis symptoms. Most early- and late-phase reactions occur in the nose after allergen exposure. The late-phase reaction is seen in chronic allergic rhinitis, with hypersecretion and congestion as the most prominent symptoms. When priming occurs, it exhibits a lowered threshold to stimulus after repeated allergen exposure that, in turn, causes a hypersensitivity reaction to one or more allergens. Sufferers may also become hyper-reactive to non-specific triggers such as cold air or strong odors. Saline sprays are generally used to relieve mucosal irritation or dryness associated with various nasal conditions, minimize mucosal atrophy, and dislodge encrusted or thickened mucus and are used immediately before intranasal corticosteroid dosing to prevent drug-induced local irritation. Anti-histamines such as terfenadine and astemizole, two non-sedating anti-histamines, are also employed to treat this condition, but have been associated with a ventricular arrhythmia known as Torsades de Points, usually in interaction with other medications such as ketoconazole and erythromycin, or secondary to an underlying cardiac problem. Loratadine, another non-sedating anti-histamine, and cetirizine have not been associated with an adverse impact on the QT interval, or with serious adverse cardiovascular events. Cetirizine, however, produces extreme drowsiness and has not been widely prescribed. Non-sedating anti-histamines, e.g. Claritin have not been tested for asthma or other more specific conditions. Terfenadine, loratadine and astemizole, on the other hand, exhibit extremely modest bronchodilating effects, reduction of bronchial hyper-reactivity to histamine, and protection against exercise- and antigen-induced bronchospasm. Some of these benefits, however, require higher-than-currently-recommended doses. The sedating-type anti-histamines help induce night sleep, but they cause sleepiness and compromise performance if taken during the day.

When employed, anti-histamines are typically combined with a decongestant to help relieve nasal congestion. Sympathomimetic medications are used as vasoconstrictors and decongestants. The three commonly prescribed systemic decongestants, pseudoephedrine, phenylpropanolamine and phenylephrine cause hypertension,

palpitations, tachycardia, restlessness, insomnia and headache. The interaction of phenylpropanolamine with caffeine, in doses of two to three cups of coffee, may significantly raise blood pressure. In addition, medications such as pseudoephedrine may cause hyperactivity in children. Topical decongestants, nevertheless, are only indicated for a limited period of time, as they are associated with a rebound nasal dilatation with overuse. Anti-cholinergic agents are given to patients with significant rhinorrhea or for specific conditions such as "gustatory rhinitis", usually caused by ingestion of spicy foods, and may have some beneficial effects on the common cold. Cromolyn used prophylactically as a nasal spray, however, produces sneezing, transient headache, and even nasal burning. Topical corticosteroids, such as Vancenase, are somewhat effective in the treatment of rhinitis, especially for symptoms of congestion, sneezing, and runny nose. Corticosteroid nose sprays, however, sometimes, cause irritation, stinging, burning and sneezing, and sometimes local bleeding and septal perforation. The side effects of topical steroids, however, limit their usefulness except for temporary therapy in patients with severe symptoms. These agents are sometimes used for shrinking nasal polyps when local therapy fails. Immunotherapy is expensive and inconvenient, and used mostly in in-patients who experience side effects from other medications. The so-called blocking antibodies, and agents that alter cellular histamine release, in addition, decrease IgE, which is useful in IgE-mediated diseases, e.g., hypersensitivity in atopic patients with recurrent middle ear infections. For allergic rhinitis sufferers, however, a runny nose is more than a nuisance. The disorder often results in impaired quality of life and sets the stage for more serious ailments, including psychological problems. Presently, rhinitis is mostly treated with propranolol, verapamil, and adenosine, all of which have Food and Drug Administration-approved labeling for acute termination of SupraVentricular Tachycardia (SVT).

There is very little currently available to alleviate symptoms of COPD, prevent exacerbations, preserve optimal lung function, and improve daily living activities and quality of life. Anti-cholinergic drugs achieve short-term bronchodilation, but no improved long-term prognosis even with inhaled products. Most COPD patients have at least some airways obstruction, and "the lung health study" found spirometric signs of early COPD in men and women smokers. Smoking cessation produced a slowing of the decline in the functional effective volume of the lungs. While ipratropium bromide was found to have no significant effect on the decline in the functional effective volume of the patient's lungs. Ipratropium bromide, however, produced serious adverse effects, such as cardiac symptoms, hypertension, skin rashes, and urinary retention. Short and long acting inhaled  $\beta_2$  adrenergic agonists achieve short-term bronchodilation and provide some symptomatic relief in COPD patients, but show no meaningful maintenance effect on its progression. Short acting  $\beta_2$  adrenergic agonists increase exercise capacity and produce some degree of bronchodilation, and even increase lung function in some severe COPD cases. The maximum effectiveness of the newer long acting inhaled  $\beta_2$  adrenergic agonists was found to be comparable to that of short acting  $\beta_2$  adrenergic agonists. Salmeterol was found to produce modest or no change in lung function. In asthmatics, moreover,  $\beta_2$  adrenergic agonists have been linked to an increased risk of death, worsened control of asthma, and deterioration in lung function.

Continuous treatment of asthmatic and COPD patients with the bronchodilators ipratropium bromide or fenoterol resulted in a decline in lung function, therefore indicating that they are not suitable for maintenance treatment. The most common immediate adverse effect of  $\beta_2$  adrenergic agonists, however, is tremors, which at high doses may cause a fall in plasma potassium, dysrhythmias, and reduced arterial oxygen tension. The combination of a  $\beta_2$  adrenergic agonist with an anti-cholinergic drug provides little additional bronchodilation compared with either drug alone. Theophyllines have a small bronchodilatory effect in COPD patients but common adverse effects, such as nausea, diarrhea, headache, irritability, seizures, and cardiac arrhythmias, that occur at highly variable blood concentrations and, in many people, within the therapeutic range. In addition, they have a small therapeutic range given that blood concentrations of 15-20 mg/l are required for optimal effects. The theophylline dose must be adjusted individually based on smoking habits, infection, and other treatments, which is cumbersome. No inflammatory response to theophyllines, however, has been reported in COPD. Oral corticosteroids show some improvement in baseline functional effective volume in stable COPD patients whereas systemic corticosteroids have been found to produce some degree of osteoporosis and overt diabetes. The longer term use of oral corticosteroids may be useful in COPD, but its usefulness must be weighed against their substantial adverse effects. Inhaled corticosteroids have been found to have no significant short-term effect in airway hyper-responsiveness to histamine, but a small long-term effect on lung function, e.g., in pre-bronchodilator functional effective volume. The treatment of COPD patients with fluticasone showed a significant reduction in moderate and severe exacerbations, and a small but significant improvement in lung function and six minute walking distance. Oral prednisolone, inhaled

5 beclomethasone or their combination had no effects in COPD patients, but lung function improved oral corticosteroids. Mucolytics have a modest effect on frequency and duration of exacerbations but an adverse effect on lung function. No mucolytics, however, have a significant effect in people with severe COPD. N-acetylcysteine, moreover, produced gastrointestinal side effects. Long-term oxygen therapy administered to hypoxaemic COPD and congestive cardiac failure patients, had little effect on death in men. In women, however, oxygen decreased the rates of death.

10 Although the progress and symptoms of pulmonary fibrosis and other ILDs may vary from person to person, they have one common link: they affect parts of the lung. The inflammation of the walls of the bronchioles (small airways), it is called bronchiolitis, and of the walls and air spaces of the alveoli (air sacs), it is called alveolitis. When the inflammation involves the small blood vessels (capillaries) of the lungs, it is called vasculitis. The inflammation may heal, or it may lead to permanent scarring of the lung tissue (pulmonary fibrosis). This latter results in permanent loss of the tissues ability to breathe and carry oxygen, and the amount of scarring determines the level of disability a person experiences due to destruction of the air sacs and lung tissue between and surrounding the air sacs and the lung capillaries. When this happens, oxygen is generally administered to help  
15 improve breathing. Pulmonary fibrosis is generally caused by occupational and environmental exposure to irritants such as asbestos, silica and metal dusts, bacteria and animal dusts, gases and fumes, asbestosis and silicosis, infections that produce lung scarring, e.g., tuberculosis, connective or collagen tissue diseases such as Rheumatoid Arthritis, Systemic Sclerosis and Systemic Lupus Erythematosus, Idiopathic Pulmonary Fibrosis, Pulmonary Fibrosis of genetic/familial origin, and certain medicines. Many of the diseases are often named after the occupations with  
20 which they are associated, such as Grain handler's lung, Mushroom worker's lung, Bagassosis, Detergent worker's lung, Maple bark stripper's lung, Malt worker's lung, Paprika splitter's lung, and Bird breeder's lung.

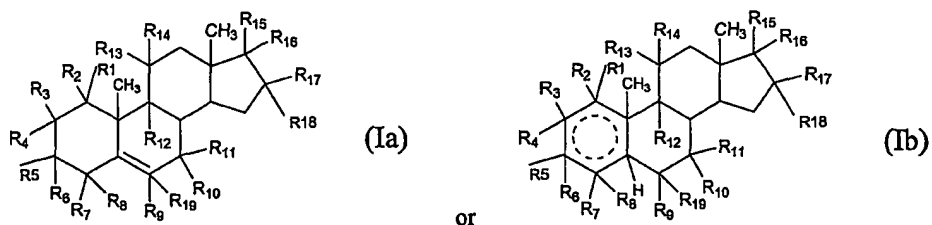
"Idiopathic" (of unknown origin) pulmonary fibrosis (IPF) is the label applied when all other causes of interstitial lung disease have been ruled out, and is said to be caused by viral illness and allergic or environmental exposure (including tobacco smoke). Bacteria and other microorganisms are not thought to be a cause of IPF. There  
25 is also a familial form of the disease, known as familial idiopathic pulmonary fibrosis whose main symptom is shortness of breath. Since many lung diseases show this symptom, making a correct diagnosis is often difficult. The shortness of breath may first appear during exercise and the condition may progress then to the point where any exertion is impossible. Eventually resulting in shortness of breath even at rest. Other symptoms may include a dry cough (without sputum), and clubbing of the fingertips. Glucocorticosteroids are usually administered to treat  
30 inflammation with inconclusive results. Other drugs are added when it is clear that the steroids are ineffective. Glucocorticosteroids are also used in combination with, for example, oxygen therapy in severe cases. Infection is prevented by administration of influenza and pneumococcal pneumonia vaccines. Lung biopsies are employed to assess the unpredictable response of patients to glucocorticosteroids or other immune system suppressants. Lung transplants are an ultimate option in severe cases of pulmonary fibrosis and other lung diseases. Pulmonary fibrosis  
35 may be caused by other specific diseases, such as sarcoidosis, a disease characterized by the formation of granulomas or areas of inflammatory cells, that may attack any organ of the body, most frequently the lungs, and shows enlarged lymph glands in the center of both lungs or lung tissue thickening. For many patients, sarcoidosis is a minor problem. Its symptoms including dry cough, shortness of breath, mild chest pain, fatigue, and weakness, and weight loss appears infrequently and stops even without medication. For others, it is a serious, disabling disease.  
40 Although almost everybody may develop the disease, it affects African-Americans more than members of any other race, most commonly young adults 20 to 40. Histiocytosis X, also associated with pulmonary fibrosis, seems to begin in the bronchioles or small airways of the lungs and their associated arteries and veins, and is generally followed by destruction of the bronchioles and narrowing and damaging of small blood vessels. Symptoms of this disease include a dry cough (without sputum), breathlessness upon exertion, and/or chest pain. In most cases the  
45 disease is chronic with loss of lung function, and glucocorticosteroid therapy is ineffective. Many histiocytosis X sufferers are current or former cigarette smokers mining workers, those exposed to asbestos or metal dusts or fibers, and agricultural workers exposed to particulate organic substances, such as moldy hay (Farmer's Lung). Asbestosis and silicosis are two occupational lung diseases whose causes are known. Asbestosis is caused by small needle-like particles of asbestos inhaled into the lungs that cause lung scarring or pulmonary fibrosis that may lead to lung  
50 cancer. Silicosis is a dust disease that comes from breathing in free crystalline silica dust, and is produced by all types of mining in which the ore, e. g. gold, lead, zinc, copper, iron, anthracite (hard) coal, and some bituminous (soft) coal, are extracted from quartz rock. Workers in foundries, sandstone grinding, tunneling, sandblasting,

concrete breaking, granite carving, and china manufacturing also inhaled tiny specks of silica that are carried down to the lung alveoli, where they lead to pulmonary fibrosis. There is no good therapy for this disease, but glucocorticosteroids alone, or combined drug therapy, and the hope of lung transplant are three treatments currently being tested. This patent provides the first effective therapy for these and other respiratory and lung ailments.

In the present context, the terms “adenosine, surfactant and ubiquinone depletion” are intended to encompass levels that are lowered or depleted in the subject as compared to previous levels in that subject, and levels, as well as levels in that subject but, because of some other reason, a therapeutic benefit would be achieved in the patient by modification of the levels of these agents as compared to previous levels.

The present invention, thus, provides a pharmaceutical or veterinary composition, comprising a pharmaceutically or veterinarily acceptable carrier or diluent, a first active agent comprising an anti-sense oligonucleotide(s) (oligo(s)), and a second active agent comprising an anti-inflammatory steroid and/or a ubiquinone, in amounts effective for alleviating a variety of airway or lung diseases, and other diseases such as cancers or their metastasis, among others. This invention provides the targeted administration of one or more oligo(s) in combination with a second active agent that has a more generalized effect as an anti-inflammatory, and alleviates bronchoconstriction, surfactant or ubiquinone depletion, and respiratory airway allergies. The oligos may be directed to one or more of a number of targets, and are delivered by any route, preferably through the airways to attain a fast and localized delivery through the mucosal tissue of the lungs to permit their hybridization to a desired target polynucleotide to prevent gene transcription and/or translation, thereby reducing, hampering or completely stopping gene expression. This may be attained by means of a solid powdered or liquid solution, suspension or emulsion, such as an aerosol, for administration into the respiratory airways, or direct instillation into the lung(s). While both active agents may be administered via the respiration, it is also possible to administer one by another route, e.g. steroids. The oligos employed in the composition are suitable for altering effects mediated by a variety of target polynucleic acids, such as regulatory nucleic acid sequences, genes and mRNAs, that are associated with diseases and conditions affecting the pulmonary and respiratory tracts, among others, and their associated effects, e.g. bronchoconstriction, respiratory tract inflammation, immune mediated reactions, lung surfactant deficiency(ies), respiratory allergy(ies) and other airway problems, which may be caused by different conditions, including pulmonary vasoconstriction, inflammation, respiratory allergies, asthma, impeded respiration, respiratory distress syndrome (RDS), pain, cystic fibrosis (CF), allergic rhinitis, pulmonary hypertension and fibrosis, sepsis, dispnea, acute respiratory distress syndrome (ARDS), as well as its variations in pregnant mothers and new-borns (RDS), pulmonary fibrosis, emphysema, chronic obstructive pulmonary disease (COPD), bronchitis, and cancers such as leukemias, lymphomas, carcinomas, and the like, e.g. lung cancer, colon cancer, breast cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer. The present agents are also suitable for administration before, during and after other treatments, including radiation, chemotherapy, antibody therapy, phototherapy, and cancer and other surgeries.

The second active agent is selected from an anti-inflammatory steroid such as an adrenal androgen of the chemical formula



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub> and R<sub>19</sub> are independently H, OR, halogen, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>) alkene, (C<sub>1</sub>-C<sub>10</sub>) alkyne, (C<sub>1</sub>-C<sub>10</sub>) alkoxy, or two or more of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub> and R<sub>19</sub> can be linked by combination of the atoms of C, O, N, S, P and Si to form a 3 to 15 member ring(s), in the  $\alpha$ - and/or  $\beta$ - configuration;

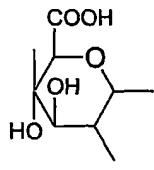
R<sub>5</sub>, R<sub>6</sub>, R<sub>10</sub>, and R<sub>11</sub> are independently OH, SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane, -OSO<sub>2</sub>R<sub>20</sub>, -OPOR<sub>20</sub>R<sub>21</sub>, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>) alkene, (C<sub>1</sub>-C<sub>10</sub>) alkyne or OR<sub>23</sub>,  

$$\begin{array}{c} \text{-SO}_2\text{O-CH}_2\text{CHCH}_2\text{OCOR}_{25} \\ | \\ \text{OCOR}_{24} \end{array}$$

- 5 wherein, R<sub>23</sub> is hydrogen or SO<sub>2</sub>OM, wherein M is selected from H, Na, sulfate;  

$$\begin{array}{c} \text{-PO}_2\text{O-CH}_2\text{CHCH}_2\text{OCOR}_{25} \\ | \\ \text{OCOR}_{24} \end{array}$$

phosphatide , wherein R<sub>24</sub> and R<sub>25</sub>, which may be the same or different, are straight or branched (C<sub>1</sub>-C<sub>20</sub>) alkyl, (C<sub>1</sub>-C<sub>20</sub>) alkene, (C<sub>1</sub>-C<sub>20</sub>) alkyne, sugar, polyethyleneglycol (PEG) or glucuronide



R<sub>5</sub> and R<sub>6</sub> taken together are =O;

- 10 R<sub>10</sub> and R<sub>11</sub> taken together are =O;

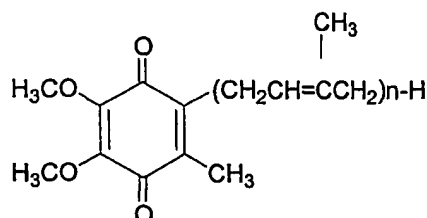
R<sub>15</sub> is (1) H, halogen, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>) alkene, (C<sub>1</sub>-C<sub>10</sub>) alkyne, or (C<sub>1</sub>-C<sub>10</sub>) alkoxy when R<sub>16</sub> is -C(O)OR<sub>22</sub>, (2) H, halogen, OH, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>) alkene or (C<sub>1</sub>-C<sub>10</sub>) alkyne, when R<sub>16</sub> is halogen, OH, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>) alkene or (C<sub>1</sub>-C<sub>10</sub>) alkyne, (3) H, halogen, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>) alkenyl, (C<sub>1</sub>-C<sub>10</sub>) alkynyl, formyl, (C<sub>1</sub>-C<sub>10</sub>) alkanoyl or epoxy when R<sub>16</sub> is OH, (4) OR, SR, SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane, -OSO<sub>2</sub>R<sub>20</sub> or -OPOR<sub>20</sub>R<sub>21</sub> when R<sub>16</sub> is H, or R<sub>15</sub> and R<sub>16</sub> taken together are =O;

20

R<sub>17</sub> and R<sub>18</sub> are independently (1) H, -OH, halogen, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>) alkene, (C<sub>1</sub>-C<sub>10</sub>) alkyne or -(C<sub>1</sub>-C<sub>10</sub>) alkoxy when R<sub>6</sub> is H OR, halogen, (C<sub>1</sub>-C<sub>10</sub>) alkyl or -C(O)OR<sub>22</sub>, (2) H, (C<sub>1</sub>-C<sub>10</sub>) alkyl)<sub>n</sub> amino, (C<sub>1</sub>-C<sub>10</sub>) alkene)<sub>n</sub> amino, (C<sub>1</sub>-C<sub>10</sub>) alkyne)<sub>n</sub> amino, ((C<sub>1</sub>-C<sub>10</sub>) alkyl)<sub>n</sub> amino-(C<sub>1</sub>-C<sub>10</sub>) alkyl, ((C<sub>1</sub>-C<sub>10</sub>) alkene)<sub>n</sub> amino-(C<sub>1</sub>-C<sub>10</sub>) alkyl, ((C<sub>1</sub>-C<sub>10</sub>) alkyne)<sub>n</sub> amino-(C<sub>1</sub>-C<sub>10</sub>) alkyl, ((C<sub>1</sub>-C<sub>10</sub>) alkyl)<sub>n</sub> amino-(C<sub>1</sub>-C<sub>10</sub>) alkene, ((C<sub>1</sub>-C<sub>10</sub>) alkene)<sub>n</sub> amino-(C<sub>1</sub>-C<sub>10</sub>) alkene, ((C<sub>1</sub>-C<sub>10</sub>) alkyne)<sub>n</sub> amino-(C<sub>1</sub>-C<sub>10</sub>) alkyne, ((C<sub>1</sub>-C<sub>10</sub>) alkene)<sub>n</sub> amino-(C<sub>1</sub>-C<sub>10</sub>) alkyne, ((C<sub>1</sub>-C<sub>10</sub>) alkyne)<sub>n</sub> amino-(C<sub>1</sub>-C<sub>10</sub>) alkyne, (C<sub>1</sub>-C<sub>10</sub>) alkoxy, hydroxy - (C<sub>1</sub>-C<sub>10</sub>) alkyl, hydroxy - (C<sub>1</sub>-C<sub>10</sub>) alkene, hydroxy - (C<sub>1</sub>-C<sub>10</sub>) alkyne, (C<sub>1</sub>-C<sub>10</sub>) alkoxy - (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>) alkoxy - (C<sub>1</sub>-C<sub>10</sub>) alkene, (C<sub>1</sub>-C<sub>10</sub>) alkoxy - (C<sub>1</sub>-C<sub>10</sub>) alkyne, (halogen)<sub>m</sub> (C<sub>1</sub>-C<sub>10</sub>) alkyl, (halogen)<sub>m</sub> (C<sub>1</sub>-C<sub>10</sub>) alkene, (halogen)<sub>m</sub> (C<sub>1</sub>-C<sub>10</sub>) alkyne, (C<sub>1</sub>-C<sub>10</sub>) alkanoyl, formyl, (C<sub>1</sub>-C<sub>10</sub>) carbalkoxy or (C<sub>1</sub>-C<sub>10</sub>) alkanoyloxy when R<sub>15</sub> and R<sub>16</sub> taken together are =O, (3) R<sub>17</sub> and R<sub>18</sub> taken together are =O; (4) R<sub>17</sub> and R<sub>18</sub> taken together with the carbon to which they are attached form a 3-6 member ring containing 0 or 1 oxygen atom; or (5) R<sub>15</sub> and R<sub>17</sub> taken together with the carbons to which they are attached form an epoxide ring; R<sub>20</sub> and R<sub>21</sub> are independently OH, pharmaceutically acceptable ester or pharmaceutically acceptable ether; R<sub>22</sub> is H, (halogen)<sub>m</sub> (C<sub>1</sub>-C<sub>10</sub>) alkyl, (halogen)<sub>m</sub> (C<sub>1</sub>-C<sub>10</sub>) alkene, (halogen)<sub>m</sub> (C<sub>1</sub>-C<sub>10</sub>) alkyne, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>) alkene or (C<sub>1</sub>-C<sub>10</sub>) alkyne; n is 0, 1 or 2; and m is 1, 2 or 3; or pharmaceutically or veterinarily acceptable salts thereof; and/or

35

a ubiquinone of the chemical formula



(III)

(CoQ<sub>n</sub>),

wherein n is 1 to 12, the agent being present in an amount effective for treating respiratory lung diseases and conditions, or for reducing levels of, or sensitivity to, adenosine in a subject's tissue (s); and/or pharmaceutically acceptable salts of either of them.

One group of preferred steroids having a general formula (Ib) are 21-acetoxypregnenolone ((3 $\beta$ )-21-(acetyloxy)-3-hydroxypregn-5-en-20-one; Herloff and Inhoffen, US Patent No. 2,409,043); alclometasone ((7 $\alpha$ , 11 $\beta$ , 16 $\alpha$ )-7-Chloro-11, 17, 21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione; Green et al., US Patent No. 4,076,708, and Green and Shue, US Patent No. 4,124,707), or its 17,21-dipropionate form (C<sub>28</sub>H<sub>37</sub>ClO<sub>7</sub>); algestone ((16 $\alpha$ )-16,17-dihydroxypregn-4-ene-3,20-dione; Colton, US Patent No. 2,727,909, Hydorn et al., US Patent No. 3,165,541, and Diassi, US Patent No. 3,027,384), its cyclic acetal with acetone form (C<sub>24</sub>H<sub>34</sub>O<sub>4</sub>), or its 16 $\alpha$ -methyl ether form (C<sub>22</sub>H<sub>32</sub>O<sub>4</sub>); amcinonide ((11 $\beta$ , 16 $\alpha$ )-21-(acetyloxy)-16,17-[cyclopentylidenebis(oxy)]-9-fluoro-11-hydroxypregna-1,4-diene-3,20-dione; Shultz et al., German Patent No. 2,437,847); beclomethasone ((11 $\beta$ , 16 $\beta$ )-9-chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione; British Patent No. 912,378, British Patent No. 901,093, Elks et al., Belgium Patent No. 649,170, and US Patent No. 3,312,590), its dipropionate form (C<sub>28</sub>H<sub>37</sub>ClO<sub>7</sub>), or its monopropionate form; betamethasone ((11 $\beta$ , 16 $\beta$ )-9-fluoro-11, 17, 21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione; US Patent No. 3,053,865, and Amiard et al., US Patent No. 3,104,246), its 21-acetate form (C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub>), its 21-adamantoate form (C<sub>33</sub>H<sub>43</sub>FO<sub>6</sub>; Philips and English, German Patent No. 2,232,827), its 17-benzoate form (C<sub>29</sub>H<sub>33</sub>FO<sub>6</sub>), its 17, 21-dipropionate form (C<sub>28</sub>H<sub>37</sub>FO<sub>7</sub>), its 17-valerate form (C<sub>27</sub>H<sub>37</sub>FO<sub>6</sub>; Dutch Patent Application No. 6,406,615), or its 21-phosphate disodium salt form (C<sub>22</sub>H<sub>28</sub>FNa<sub>2</sub>O<sub>8</sub>P); budesonide ((11 $\beta$ , 16 $\alpha$ )-16,17-[butylidenebis(oxy)]-11, 21-dihydropregna-1,4-diene-3,20-dione; Brattsand et al., German Patent No. 2,323,215, and US Patent No. 3,929,768); chloroprednisone ((6 $\alpha$ )-chloro-17,21-dihydroxypregna-1,4-diene-3,11,20-trione; Batres et al., German Patent No. 1,079,042, and Ringold and Rosenkrantz, US Patent No. 2,957,895), or its 21-acetate form (C<sub>23</sub>H<sub>27</sub>ClO<sub>6</sub>); ciclesonide (Taylor et al., Am J Respir Crit Care Med (1999) 160(1), 237-43); clobetasol ((11 $\beta$ , 16 $\beta$ )-21-chloro-9-fluoro-11,17-dihydroxy-16-methylpregna-1,4-diene-3,20-dione; Elks et al., German Patent No. 1,902,340, and US Patent No. 3,721,687), or its 17-propionate form (C<sub>25</sub>H<sub>32</sub>ClFO<sub>5</sub>); clobetasone ((16 $\beta$ )-21-chloro-9-fluoro-17-hydroxy-16-methylpregna-1,4-diene-3,11,20-trione; Elks et al., German Patent No. 1,902,340, and US Patent No. 3,721,687), or its 17-butyrate form (C<sub>26</sub>H<sub>32</sub>ClFO<sub>5</sub>); clocortolone ((6 $\alpha$ , 11 $\beta$ , 16 $\alpha$ )-9-chloro-6-fluoro-11,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione; Dutch Patent Application No. 6,412,708, Kasper and Philippson, German Patent No. 2,011,559, and US Patent No. 3,729,495), its 21-acetate form (C<sub>24</sub>H<sub>30</sub>ClFO<sub>5</sub>), or its 21-pivalate form (C<sub>27</sub>H<sub>36</sub>ClFO<sub>5</sub>); cloprednol ((11 $\beta$ )-6-chloro-11,17,21-trihydroxypregna-1,4,6-triene-3,20-dione; France Patent No. 1,271,981, and US Patent No. 3,232,965); coroxon (phosphoric acid 3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl diethyl ester; Fusco et al., US Patent No. 2,951,851); cortisone (17,21-dihydroxypregn-4-ene-3,11,20-trione; Reichstein, US Patent No. 2,403,683, and Gallagher, US Patent No. 2,447,325), its 21-acetate form (C<sub>23</sub>H<sub>30</sub>O<sub>6</sub>), or its 21-cyclopentanepropionate form (C<sub>29</sub>H<sub>40</sub>O<sub>6</sub>), examples of brand name for cortisone include Cortone Acetate, Adreson, Altesona, Cortelan, Cortistab, Cortisyl, Cortogen, Cortone, and Scheroson; cortivazol ((11 $\beta$ , 16 $\alpha$ )-21-(acetyloxy)-11,17-dihydroxy-6,16-dimethyl-2'-phenyl-2'H-pregna-2,4,6-trieno[3,2-c]pyrazol-20-one; Tishler et al., US Patent No. 3,067,194, and US Patent No. 3,300,483); deflazacort ((11 $\beta$ , 16 $\beta$ )-21-(acetyloxy)-11-hydroxy-2'-methyl-5'H-pregna-1,4-dieno[17,16-d]oxazole-3,20-dione; Nathansohn and Winters, Belgium Patent No. 679,820, British Patent No. 1,077,393, and US Patent No. 3,436,389); desonide ((11 $\beta$ , 16 $\alpha$ )-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione; Bernstein and Allen, US Patent No. 2,990,401, Lee et al., US Patent No. 3,536,586, and Diassi and Principe, US Patent No. 3,549,498); desoximetasone ((11 $\beta$ , 16 $\alpha$ )-9-fluoro-11, 21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione; Joly et al., France Patent No. 1,296,544, US Patent No. 3,099,654, Belgium Patent No. 614,196, and Kieslich et al., US Patent No. 3,232,839); dexamethasone ((11 $\beta$ , 16 $\alpha$ )-9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione; Muller et al., US Patent No. 3,007,923, Arth et al., German Patent No. 1,113,690, and British Patent No. 869,511), its 21-acetate form (C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub>), its 21-(3,3-dimethylbutyrate) form (C<sub>28</sub>H<sub>39</sub>FO<sub>6</sub>; Chemerda et al., US Patent No. 2,939,873), its 21-diethylaminoacetate form (C<sub>28</sub>H<sub>41</sub>FNO<sub>6</sub>), its 21-isonicotinate form (C<sub>28</sub>H<sub>41</sub>FNO<sub>6</sub>), its 17,21-dipropionate form (C<sub>28</sub>H<sub>37</sub>FNO<sub>6</sub>), or its 21-palmitate form (C<sub>38</sub>H<sub>59</sub>FO<sub>6</sub>), examples of brand name for dexamethasone include Decadron-oral, Dexameth, Dexone, Hexadrol-oral, Dexamethasone Intensol, Dexone 0.5, Dexone 0.75, Dexone 1.5, and Dexone 4; diflorasone ((6 $\alpha$ , 11 $\beta$ , 16 $\beta$ )-6,9-difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione; British Patent No. 881,334, British Patent No. 898,293, Lincoln et al., US Patent No. 3,557,158, and British Patent No. 912,015), or its diacetate form (C<sub>26</sub>H<sub>32</sub>F<sub>2</sub>O<sub>7</sub>; Ayer et al., German Patent No. 2,308,731, and



US Patent No. 3,980,778); diflucortolone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6,9-difluoro-11,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione; Belgium Patent No. 639,708, and Kieslich et al., US Patent No.3,426,128), or its 21-valerate form (C<sub>27</sub>H<sub>36</sub>F<sub>2</sub>O<sub>5</sub>); difluprednate ((6 $\alpha$ ,11 $\beta$ )-21-(acetyloxy)-6,9-difluoro-11-hydroxy-17-(1-oxobutoxy)pregna-1,4-diene-3,20-dione; Ercoli and Gardi, South African Patent No. 680,386, and Ercoli et al., US Patent No. 3,780,177);

5 enoxolone ((3 $\beta$ ,20 $\beta$ )-3-hydroxy-11-oxoolean-12-en-29-oic acid; British Patent No. 833,184), or its 18 $\alpha$ -hydrogen form; fluazacort ((11 $\beta$ ,16 $\beta$ )-21-(acetyloxy)-9-fluoro-11-hydroxy-2'-methyl-5'H-pregna-1,4-dieno[17,16-d]oxazole-3,20-dione; British Patent No. 1,119,082, and US Patent No. 3,461,119); flucoronide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-9,11-dichloro-6-fluoro-21-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione; Bowers, US Patent No. 3,201,391); flumethasone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6,9-difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione;

10 British Patent No. 902,292, and Lincoln et al., US Patent No. 3,499,016), its 21-acetate form (C<sub>24</sub>H<sub>30</sub>F<sub>2</sub>O<sub>6</sub>), or its 21-pivalate form (C<sub>27</sub>H<sub>36</sub>F<sub>2</sub>O<sub>6</sub>); flunisolide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione; British Patent No. 933,867, Ringold and Rosenkranz, US Patent No. 3,124,571, and Ringold et al., US Patent No. 3,126,375), or its 21-acetate form (C<sub>26</sub>H<sub>33</sub>FO<sub>7</sub>); fluocinolone acetate ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione;

15 Mills and Bowers, US Patent No. 3,014,938, and Ringold et al., US Patent No. 3,126,375); fluocinonide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-21-(acetyloxy)-6,9-difluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione; British Patent No. 916,996, Ringold and Rosenkranz, US Patent No. 3,124,571, Ringold et al., US Patent No. 3,126,375, and Fried, US Patent No. 3,197,469); fluocortin butyl ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11-hydroxy-16-methyl-3,20-dioxopregna-1,4-dien-21-oic acid butyl ester; Laurent et al., German Patent Nos. 2,150,268 and

20 2,150,270, and US Patent No. 3,824,260); fluocortolone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione; Belgium Patent 614,196, and Kieslich et al., US Patent No. 3,232,839), its 21-acetate form (C<sub>24</sub>H<sub>31</sub>FO<sub>5</sub>), its 21-hexanoate form (C<sub>28</sub>H<sub>39</sub>FO<sub>5</sub>), or its 21-pivalate form (C<sub>22</sub>H<sub>37</sub>FO<sub>5</sub>); fluorometholone ((6 $\alpha$ ,11 $\beta$ )-9-fluoro-11,17-dihydroxy-6-methylpregna-1,4-diene-3,20-dione; Lincoln et al., US Patent No. 2,867,637), or its 17-acetate form (C<sub>24</sub>H<sub>31</sub>FO<sub>5</sub>; Magerlein et al., US Patent No. 3,038,914); fluperolone acetate ([11 $\beta$ ,17 $\alpha$ ,17(S)]-17-[2-(acetyloxy)-1-oxopropyl]-9-fluoro-11,17-dihydroxyandrost-1,4-dien-3-one; Agnello and Laubach, US Patent No. 3,234,095); fluprednidene acetate ((11 $\beta$ )-21-(acetyloxy)-9-fluoro-11,17-dihydroxy-16-methylenepregna-1,4-diene-3,20-dione; Wendler et al., US Patent Nos. 3,065,239, 3,068,224, 3,068,226 and 3,136,760); fluprednisolone ((6 $\alpha$ ,11 $\beta$ )-6-fluoro-11,17,21-trihydroxypregna-1,4-diene-3,20-dione; Batres et al., German Patent No. 1,079,042, and Lettre and Hotz, German Patent No. 1,088,953), or its 21-acetate form (C<sub>23</sub>H<sub>29</sub>FO<sub>6</sub>); flurandrenolide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregn-4-ene-3,20-dione; Ringold et al., German Patent No. 1,131,213, and US Patent No. 3,126,375); fluticasone propionate ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ ,17 $\alpha$ )-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androst-1,4-diene-17-carbothioic acid S-(fluoromethyl) ester; Dutch Patent Application No. 8,100,707, and Phillipps et al., US Patent No. 4,335,121); formocortol ((11 $\beta$ ,16 $\alpha$ )-21-(acetyloxy)-3-(2-chloroethoxy)-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-20-

35 oxopregna-3,5-diene-6-carboxaldehyde; Camerino et al., France Patent No. 1,396,602, Dutch Patent Application No. 6,508,458, and US Patent No. 3,314,945); halcinonide ((11 $\beta$ ,16 $\alpha$ )-21-chloro-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregn-4-ene-3,20-dione; Difazio and Augustine, German Patent No. 2,355,710, and US Patent No. 3,892,857); halobetasol propionate (6 $\alpha$ ,11 $\beta$ ,16 $\beta$ )-21-chloro-6,9-difluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)pregna-1,4-diene-3,20-dione; Kalvoda and Anner, German Patent No. 2,743,069, and US Patent No.

40 4,619,921); halometasone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-2-chloro-6,9-difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione; Anner et al., Dutch Patent Application No. 540,244, US Patent No. 3,652,554, and Swiss Patent No. 551,399), or its monohydrate form (C<sub>22</sub>H<sub>27</sub>ClF<sub>2</sub>O<sub>5</sub>•H<sub>2</sub>O); halopredone acetate ((6 $\beta$ ,11 $\beta$ )-17,21-bis(acetyloxy)-2-bromo-6,9-difluoro-11-hydroxypregna-1,4-diene-3,20-dione; Riva and Toscano, German Patent No. 2,508,136, and Riva et al., US Patent No. 4,226,862); hydrocortamate (N,N-diethylglycine (11 $\beta$ )-11,17-dihydroxy-3,20-dioxopregn-4-en-21-yl ester; Pinson and Laubach, German Patent No. 1,016,708, and Richter and Schenck, German Patent No. 1,037,451), or its hydrochloride form (C<sub>27</sub>H<sub>41</sub>NO<sub>6</sub>•HCl); hydrocortisone ((11 $\beta$ )-11,17,21-trihydroxypregn-4-ene-3,20-dione; Murray and Peterson, US Patent No. 2,602,769), its 21-acetate form (C<sub>23</sub>H<sub>32</sub>O<sub>6</sub>), its 17-butyrate form (C<sub>25</sub>H<sub>36</sub>O<sub>6</sub>), its 21-phosphate disodium salt form (C<sub>21</sub>H<sub>29</sub>Na<sub>2</sub>O<sub>8</sub>P), its 21-sodium succinate form (C<sub>25</sub>H<sub>33</sub>NaO<sub>8</sub>), its 17-valerate form (C<sub>26</sub>H<sub>38</sub>O<sub>6</sub>), or its cypionate form (Munson and Wilson, J Pharm Sci (1981)

45 70(2), 177-81), examples of brand name for hydrocortisone include Cortef, Hydrocortone, examples of brand name for hydrocortisone cypionate include Cortef Oral Suspension; loteprednol etabonate ((11 $\beta$ ,17 $\alpha$ )-17-

[(ethoxycarbonyl)oxy]-11-hydroxy-3-oxoandrost-1,4-diene-17-carboxylic acid chloromethyl ester; Bodor, Belgium Patent No. 889,563, and US Patent No. 4,996,335); mazipredone ((11 $\beta$ )-11,17-dihydroxy-21-(4-methyl-1-piperazinyl)pregna-1,4-diene-3,20-dione; Tuba et al., Hungarian Patent No. 150,350), or its hydrochloride form (C<sub>26</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>•HCl); medrysone ((6 $\alpha$ ,11 $\beta$ )-11-hydroxy-6-methylpregn-4-ene-3,20-dione; Sebek et al., US Patent No. 2,864,837, and Spero and Thompson, US Patent No. 2,968,655); meprednisone ((16 $\beta$ )-17,21-dihydroxy-16-methylpregna-1,4-diene-3,11,20-trione; British Patent No. 901,092, and Rausser and Oliveto, US Patent No. 3,164,618), or its 21-acetate form (C<sub>24</sub>H<sub>30</sub>O<sub>6</sub>); methylprednisolone ((6 $\alpha$ ,11 $\beta$ )-11,17,21-trihydroxy-6-methylpregna-1,4-diene-3,20-dione; Sebek and Spero, US Patent No. 2,897,218, and Gould, US Patent No. 3,053,832), its 21-acetate form (C<sub>24</sub>H<sub>32</sub>O<sub>6</sub>), its 21-phosphate disodium salt form (C<sub>22</sub>H<sub>29</sub>Na<sub>2</sub>O<sub>8</sub>P), its 21-succinate sodium salt form (C<sub>26</sub>H<sub>33</sub>NaO<sub>8</sub>), or its aceponate form (C<sub>27</sub>H<sub>36</sub>O<sub>7</sub>), examples of brand name for methylprednisolone include Medrol-Oral; mometasone furoate ((11 $\beta$ ,16 $\alpha$ )-9,21-dichloro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methylpregna-1,4-diene-3,20-dione; Shapiro, European Patent Application No. 57,401, and US Patent No. 4,472,393); paramethasone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione; Edwards et al., J. Am.Chem.Soc. (1960) 82, 2318), its 21-acetate form (C<sub>24</sub>H<sub>31</sub>FO<sub>6</sub>), its disodium phosphate form, or a mixture of its 21-acetate and disodium phosphate form; prednicarbate ((11 $\beta$ )-17-[(ethoxycarbonyl)oxy]-11-hydroxy-21-(1-oxopropoxy)pregna-1,4-diene-3,20-dione; Stache et al., Germany Patent No. 2,735,110, and US Patent No. 4,242,334); prednisolone ((11 $\beta$ )-11,17,21-trihydroxypregna-1,4-diene-3,20-dione; Nobile, US Patent Nos. 2,837,464 and 3,134,718), its 21-acetate form (C<sub>23</sub>H<sub>30</sub>O<sub>6</sub>), its 21-*tert*-butylacetate form (C<sub>27</sub>H<sub>38</sub>O<sub>6</sub>; Sarrett, US Patent No. 2,736,734), its 21-hydrogen succinate form (C<sub>25</sub>H<sub>32</sub>O<sub>8</sub>), its 21-succinate sodium salt form (C<sub>25</sub>H<sub>31</sub>NaO<sub>8</sub>; Shull and Kita, German Patent No. 1,045,400), its 21-stearoylglycolate form (C<sub>41</sub>H<sub>64</sub>O<sub>8</sub>; Giraldi and Nannini, US Patent No. 3,171,846), its 21-*m*-sulfobenzoate sodium salt form (C<sub>28</sub>H<sub>31</sub>NaO<sub>9</sub>S; (11 $\beta$ )-11,17-dihydroxy-21-[(3-sulfobenzoyl)oxy]pregna-1,4-diene-3,20-dione monosodium salt; Allais and Girault, US Patent No. 3,032,568, Joly and Warnant, US Patent No. 3,037,034), or its 21-trimethylacetate form (C<sub>26</sub>H<sub>36</sub>O<sub>6</sub>; Joly and Warnant, US Patent No. 3,037,034), examples of brand name for prednisolone include Prelone, Delta-Cortef, Pediapred, Adnisolone, Cortalone, Deltacortril, Deltasolone, Deltastab, Di-Adreson F, Encortolone, Hydrocortancyl, Medisolone, Meticortelone, Opredson, Panaafcortelone, Precortisyl, Prenisolone, Scherisolone, Scherisolone; prednisolone 21-diethylaminoacetate (N,N-diethylglycine (11 $\beta$ )-11,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl ester; British Patent No. 862,370), or its hydrochloride form (C<sub>27</sub>H<sub>39</sub>NO<sub>6</sub>•HCl); prednisolone sodium phosphate (11,17-dihydroxy-21-(phosphonoxy)pregna-1,4-diene-3,20-dione disodium salt; Sarett, US Patent No. 2,789,117, and Elks and Philipps, US Patent No. 2,936,313); prednisone (17,21-dihydroxypregna-1,4-diene-3,11,20-trione; Oliveto and Gould, US Patent No. 2,897,216, and Nobile, US Patent Nos. 2,837,464 and 3,134,718), or its 21-acetate form (C<sub>23</sub>H<sub>28</sub>O<sub>6</sub>), examples of brand name for prednisone include Deltasone, Liquid Pred, Meticorten, Orasone 1, Orasone 5, Orasone 10, Orasone 20, Orasone 50, Prednicen-M, Prednisone Intensol, Sterapred, Sterapred DS, Adasone, Cartancyl, Colisone, Cordrol, Cortan, Dacortin, Decorti, Decortisyl, Delcortin, Dellacort, Delta-Dome, Deltacortene, Deltisona, Diadreson, Econosone, Encorton, Fernisone, Nisona, Novoprednisone, Panafcort, Panasol, Paracort, Parmenison, Pehacort, Predeltin, Prednicort, Prednicot, Prednidib, Predniment, Rectodelt, Ultracorten, Winpred; prednival ((11 $\beta$ )-11,21-dihydroxy-17-[(1-oxopentyl)oxy]pregna-1,4-diene-3,20-dione; Ercoli and Gardi, US Patent No. 3,152,154), or its 21-acetate form (C<sub>28</sub>H<sub>38</sub>O<sub>7</sub>); prednylidene ((11 $\beta$ )-11,17,21-trihydroxy-16-methylenepregna-1,4-diene-3,20-dione; Mannhardt et al., Tetrahedron Letters (1960) 16, 21), or its 21-diethylaminoacetate hydrochloride form (C<sub>28</sub>H<sub>39</sub>NO<sub>6</sub>•HCl; German Patent No. 1,134,074); rimexolone ((11 $\beta$ ,16 $\alpha$ ,17 $\beta$ )-11-hydroxy-16,17-dimethyl-17-(1-oxopropyl)androst-1,4-dien-3-one; Dutch Patent Application No. 7,300,313, and Woods et al., US Patent No. 3,947,478); rofleponide ((22R)-6 $\alpha$ ,9 $\alpha$ -Difluoro-11 $\beta$ ,21-dihydroxy-16 $\alpha$ ,17 $\alpha$ -propylmethylenedioxypregn-4-ene-3,20-dione; Thalen and Wickstrom, Steroids (2000) 65(1), 16-23); tipredane ((11 $\beta$ , 17 $\alpha$ )-17-(ethylthio)-9 $\alpha$ -fluoro-11 $\beta$ -hydroxy-17-(methylthio) androst-1,4-dien-3-one; Wojnar et al., Arzneimittelforschung (1986) 36(12), 1782-7); tixocortol ((11 $\beta$ )-11,17-dihydroxy-21-mercaptopregn-4-ene-3,20-dione; Simons et al., J Steroid Biochem (1980) 13, 311), or its 21-pivalate form (C<sub>26</sub>H<sub>38</sub>O<sub>5</sub>S; (11 $\beta$ )-21-[(2,2-dimethyl-1-oxopropyl)thio]-11,17-dihydroxypregn-4-ene-3,20-dione; Torossian et al., German Patent No. 2,357,778, and US Patent No. 4,014,909); triamcinolone ((11 $\beta$ ,16 $\alpha$ )-9-fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione; Bernstein et al., US Patent No. 2,789,118, and Allen et al., US Patent No.3,021,347), or its 16,21-diacetate form (C<sub>25</sub>H<sub>31</sub>FO<sub>8</sub>; (11 $\beta$ ,16 $\alpha$ )-16,21-bis(acetyloxy)-9-fluoro-11,17-dihydroxypregna-1,4-diene-3,20-dione), examples of brand name for triamcinolone include Kenacort, Aristocort, Atolone, Sholog A, Tramacort-D, Tri-Med,

Triamcot, Tristo-Plex, Trylone D, U-Tri-Lone; Triamcinolone acetonide ((11 $\beta$ ,16 $\alpha$ )-9-fluoro-11,21-dihydroxy-16,17-[1-methylethylidenebis(oxy)]pregna-1,4-diene-3,20-dione; Bernstein and Allen, US Patent No. 2,990,401, and Hydrom, US Patent No. 3,035,050), its 21-acetate crystal form, its 21-disodium phosphate form (C<sub>24</sub>H<sub>30</sub>FN<sub>2</sub>O<sub>9</sub>P), or its 21-hemisuccinate form (C<sub>28</sub>H<sub>35</sub>FO<sub>9</sub>); triamcinolone benetonide ((11 $\beta$ ,16 $\alpha$ )-21-[3-(benzoylamino)-2-methyl-1-oxopropoxy]-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione; Cavazza et al., German Patent No. 2,047,218, and US Patent No. 3,749,712); and triamcinolone hexacetonide ((11 $\beta$ ,16 $\alpha$ )-21-(3,3-dimethyl-1-oxobutoxy)-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione; Nash and Naeger, US Patent No. 3,457,348). Preferably, the steroids comprises budesonide, testosterone, progesterone, estrogen, flunisolide, triamcinolone, beclomethasone, betamethasone, dexamethasone, fluticasone, methylprednisolone, prednisone, hydrocortisone, and mometasone. Another group of preferred steroids are mineralocorticoid steroids including aldosterone, deoxycorticosterone, deoxycorticosterone acetate and fludrocortisone. However, others are also suitable.

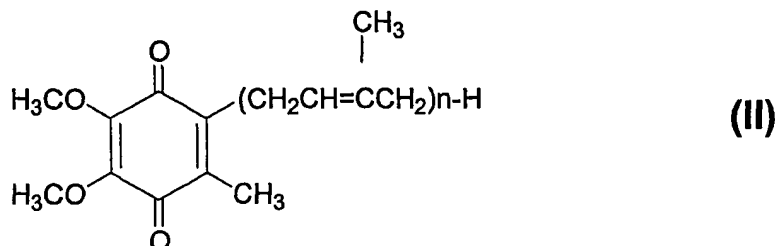
Also provided is a method for reducing or depleting adenosine levels, or treating hypersensitivity to adenosine, particularly in the lung, liver, heart and/or brain, or increasing levels of lung surfactant or of ubiquinone in the lung, heart or other tissues, and for treating various respiratory, lung and other diseases and their symptoms, by administering to a subject in need of such treatment a first active agent comprising the anti-sense oligo of the invention, and a second active agent comprising the AIS of chemical formula (Ia) and (Ib) exemplified by corticosteroids and dehydroepiandrosterones, analogues thereof, and pharmaceutically or veterinarily acceptable salts thereof, such as dehydroepiandrosterone sulfate (DHEA-S), and salts of the corticosteroids, and/or a ubiquinone of chemical formula (II) as described above, the active agents being present in amounts effective to reduce or deplete adenosine levels, or reduce adenosine hypersensitivity, or to increase lung surfactant levels or ubiquinone tissue levels, or to inhibit or control a variety of respiratory, lung and other diseases and conditions in the subject. Examples of non-glucocorticoid steroids that may be used to carry out this method are represented by the chemical formula (Ia) shown above.

Another group of preferred steroids for use in this invention are described below. The hydrogen atom at position 5 of the compound of chemical formula (Ia) may be present in the alpha or beta configuration, and the compound may comprise a mixture of both configurations. Compounds illustrative of compounds of chemical formula (I) above include DHEA, wherein R and R<sub>1</sub> each comprise hydrogen and the double bond is present; 16-alpha bromodehydroepiandrosterone, where R comprises Br, R<sub>1</sub> comprises H, and the double bond is present; 16-alpha-fluorodehydroepiandrosterone, wherein R comprises F, R<sub>1</sub> comprises H and the double bond is present; etiocholanolone, where R and R<sub>1</sub> each comprise hydrogen and the double bond is absent (the single bond is present); and dehydroepiandrosterone sulphate (DHEA-S), wherein R comprises H, R<sub>1</sub> comprises SO<sub>2</sub>OM and M comprises sulphatide as defined above, and the double bond is present, among others. In the compound of formula I, R preferably comprises halogen, e.g. bromo, chloro, or fluoro, R<sub>1</sub> comprises hydrogen, and the double bond is present. Most preferably the compound of Formula I comprises dehydroepiandrosterone sulphate and 16- $\alpha$ -fluorodehydroepiandrosterone. The compounds of formula I may be made in accordance with procedures known in the art, or employing variations thereof that will be apparent to those skilled in the art. See, for example, U.S. Patent No. 4,956,355, UK Patent No. 2,240,472, EPO Patent Application No. 429,187, Patent Publication WO9104030A1; Abou-Gharbia M. et al., J. Pharm. Sci. 70: 1154-1157 (1981), Merck Index Monograph No. 7710, 11th Ed. (1989). Other preferred non-glucocorticoid steroids are those of the formulas (III) and (IV), wherein R<sub>15</sub> and R<sub>16</sub> together are =O, or where R<sub>5</sub> is OH, or where R<sub>5</sub> is -OSO<sub>2</sub>R<sub>20</sub>, or where R<sub>20</sub> is H. Others, however, are also preferred and are encompassed by this patent.

"Corticosteroid", as used herein, means 21-carbon steroid hormone corticoids that bind to glucocorticoid receptors, having the chemical formula of (Ib). Corticosteroids are agonists for the glucocorticoid steroid receptor(s) and interact to promote a transcriptional response. The corticosteroids and other AIS may be used in conjunction with, and for reducing the amount of the oligo(s) employed for reducing inflammation and lung allergy(ies), reducing or depleting levels of, or reducing sensitivity to, adenosine, reducing adenosine receptor levels, producing bronchodilation, and/or for increasing levels of ubiquinone or lung surfactant in a subject, or for treating bronchoconstriction, lung inflammation or allergies or a respiratory or lung disease or condition. The anti-inflammatory steroid(s) may be administered per se or in the form of pharmaceutically acceptable salt, as discussed above. In general, the anti-inflammatory steroid(s), and its(their) salt(s) and crystal forms are suitable, and may be administered in a dosage of about 0.01, about 0.1, about 0.4, about 1, about 5, about 10, about 20 to about 4, about

30, about 70, about 100, about 300, about 1,000, about 3600 mg/kg body weight. These active compounds may be administered once or several times a day, or in any other regime, upon adjustment of the dose in accordance with the dosages of the other agents being administered.

The term "ubiquinone", as used herein, refers to a family of compounds having structures based on a  $\omega$  3-dimethoxy-5-methyl benzoquinone nucleus with a variable terpenoid acid chain containing on to twelve non-unsaturated trans-isoprenoid units. Such compounds are also known in the art as "Coenzyme Q<sub>n</sub>", wherein n comprises 1 to 12, preferably n comprising 1 to 10, and may be referred to herein as compounds represented by the following chemical formula



10 wherein n comprises 1 to 10. In the method of the invention, another preferred ubiquinone is a compound according to the above formula, where n comprises 6 to 10, i.e. Coenzyme Q<sub>6-10</sub>, and most preferably wherein n comprises 10, i.e. Coenzyme Q<sub>10</sub>.

As discussed above, the "active agents or compounds" may be administered per se or in the form of pharmaceutically acceptable salts, or in the same formulation with the other active agents of the invention, e.g. corticosteroid(s) and/or ubiquinone(s) and the anti-sense oligo, either systemically or topically. In general, they are administered in an amount effective to treat respiratory conditions including bronchoconstriction, respiratory inflammation and allergies, allergic rhinitis, pulmonary hypertension and fibrosis, apnea, sepsis, emphysema, cancers, asthma, COPD, RDS, CF, ARDS, and the like, and/or to off-set lung surfactant depletion or ubiquinone depletion in the lungs and/or heart of the subject if induced by the administration of the anti-inflammatory steroid of the invention. The ubiquinone is preferably administered in a total amount per day of about 0.1, about 1, about 5, about 10, about 15, about 30 to about 50, about 100, about 150, about 300, about 600, about 900, about 1200 mg/kg body weight per day. More preferred are about 1 to about 150 mg/kg, about 30 to about 100 mg/kg, and most preferred about 5 to about 50 mg/kg. The ubiquinone may be administered in one dose (once or several times a day), and its dose may be adjusted as is known in the art, depending on whether it is administered alone, or with the oligo and/or the anti-inflammatory steroid, and their amounts used. The dosage of the ubiquinone will vary depending upon the condition of the subject and route of administration. The ubiquinone may be administered by itself, or as a mixture of ubiquinones of varying side chain lengths, or concurrently, jointly prior to or subsequent to the anti-sense oligo and/or the anti-inflammatory steroid, for treating the overall symptoms described here, and/or the various diseases associated with them, including asthma, COPD, allergic rhinitis, pulmonary hypertension, vasoconstriction and fibrosis, and others described above. The phrase "concurrently administering", as used herein, means that the steroid, e. g. DHEA, DHEA-S or analogs of formulas (Ia) and (Ib), the anti-sense oligos, and the ubiquinone of chemical formula (II) are administered either (a) simultaneously in time, preferably by formulating the two active agents together in a common pharmaceutical carrier, or (b) at different times during the course of a common treatment schedule through the same or different routes of administration. In the latter case, for example the oligo may be administered once a week or its administration may be varied in accordance with its duration of action, while steroid(s) and ubiquinone(s) is(are) administered at times sufficiently close so that, in addition to its direct effect, the ubiquinone will be also off-setting any ubiquinone depletion in the subject's tissues, e. g. lungs and heart. This timing helps to prevent or counter-balance any deterioration of tissue, e. g. lung and heart, function that may result from the administration of the steroids or analogs thereof. Where the ubiquinone is formulated with a pharmaceutically acceptable carrier and other oral formulation components, it may be administered separately from the steroid and/or the oligo. For example, the steroid and the oligo may be administered into the respiration, by inhalation, nasally or into the lungs (by instillation) of the subject whereas the ubiquinone may be administered systemically. The ubiquinone may be formulated by any of the techniques set forth above.

The composition and formulations of this invention are highly efficacious for preventing and treating diseases and conditions associated with bronchoconstriction, difficult breathing, impeded and obstructed lung

airways, allergy(ies), inflammation and surfactant depletion, among others. Examples of diseases and conditions which are suitably treated by the present method are diseases and conditions, including Acute Respiratory Distress Syndrome (ARDS), asthma, adenosine administration e.g. in the treatment of SupraVentricular Tachycardia (SVT) and other arrhythmias, and in stress tests to hyper-sensitized individuals, ischemia, renal damage or failure induced by certain drugs, infantile respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), lung transplantation rejection, pulmonary infections, and cancers such as leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer. The invention will be mostly described with respect to the adenosine receptors as targets, although data on other targets is also provided, but is similarly applicable to any other target including the listed targets, with respect to the administration of anti-sense oligos. The examples provided below show a complete inhibition of adenosine receptor associated symptoms in a rabbit model for human bronchoconstriction, allergy(ies) and inflammation as well as the elimination of the ability of the adenosine receptor agonist par excellence, adenosine, to cause bronchoconstriction in hyper-responsive monkeys, which are animal models for human hyper-responsiveness to adenosine receptor agonists. The pharmaceutical composition and formulations of the invention, therefore, are suitable for preventing and alleviating the symptoms associated with stimulation of adenosine receptors, such as the adenosine  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$ , and  $A_3$  receptors, as well as other single or multiple targets. The compositions and formulations of this invention, thus, are also suitable for prevent the untoward side effects of adenosine-mediated hyperresponsiveness in certain individuals, which are generally seen in diseases affecting respiratory activity.

The method of the present invention may be used to treat airway and lung diseases and conditions in a subject of any kind and for any reason, for example, to reduced or eliminated with the intention that the adenosine content of anti-sense compounds, so as to prevent liberation of adenosine upon anti-sense degradation. Examples of diseases and conditions, which may be treated preventatively, prophylactically and therapeutically with the compositions and formulations of this invention, are pulmonary vasoconstriction, inflammation, allergies, asthma, allergic rhinitis, impeded respiration, Acute Respiratory Distress Syndrome (ARDS), renal damage and failure associated with ischemia as well as the administration of certain drugs, side effects associated with adenosine administration e.g. in SupraVentricular Tachycardia (SVT) and in adenosine stress tests, infantile Respiratory Distress Syndrome (infantile RDS), ARDS, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), lung transplantation rejection, pulmonary infections, and cancers such as leukemias, lymphomas, carcinomas, and the like, e.g. colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, metastatic cancer such as hepatic metastases, lung, breast and prostate metastases, among others. The present compositions and formulations are suitable for administration before, during and after other treatments, including radiation, chemotherapy, antibody therapy, phototherapy and cancer, and other types of surgery. The present compositions and formulations may also be administered effectively as a substitute for therapies that have significant negative side effects. The terms "anti-sense" oligonucleotides generally refers to small, synthetic oligonucleotides, resembling single- and double-stranded DNA and RNA, which in this patent are applied to the inhibition of gene expression, e.g. by inhibition of a gene or target messenger RNA (mRNA). See, e.g. Milligan, J. F. et al., J. Med. Chem. 36(14), 1923-1937 (1993); Sharp, P.A. Genes & Development 15, 485-490, 2001; the relevant portion of which is hereby incorporated in its entirety by reference. For consistency's sake, all RNAs, DNAs and oligonucleotides are represented in this patent by a single strand in the 5' to 3' or 3' to 5' direction, when read from left to right, although their complementary and double-stranded sequence(s) is (are) also encompassed within the four corners of the invention. In addition, all nucleotide bases and amino acids are represented utilizing the recommendations of the IUPAC-IUB Biochemical Nomenclature Commission, or by the known 3-letter code (for amino acids). Nucleotide sequences are presented herein by single strand only, in the 5' to 3' direction, from left to right. In addition, nucleotide and amino acids are represented herein in the manner recommended by the IUPAC-IUB Biochemical Nomenclature Commission, or (for amino acids) by three letter code, in accordance with 37 CFR ' 1.822 and established usage. See, e.g., PatentIn User Manual, 99-102 (Nov. 1990) (U.S. Patent and Trademark Office, Office of the Assistant Commissioner for Patents, Washington, D.C. 20231); U.S. Patent No. 4,871,670 to Hudson et al. at col. 3, lines 20-43. The present method utilizes anti-sense agents to inhibit or down-regulate gene expression of

target genes, including those listed in Tables 1 and 2 below. This is generally attained by hybridization of the anti-sense oligonucleotides to coding (sense) sequences of a targeted messenger RNA (mRNA), as is known in the art. The oligos of this invention may be obtained by first selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C, and then obtaining a first oligonucleotide 4 to 70 nucleotides long which comprises the selected fragment and preferably has a C and G nucleic acid content of up to and including about 20%, about 15%. The oligonucleotide(s) (oligo(s)) may include at least one unmethylated cytosine-guanine (CpG) dinucleotide. The CpG dinucleotide may be substituted for a methylated cytosine present in the anti-sense oligonucleotide(s). The CpG dinucleotide is an immunostimulating sequence and affects the immune response in a subject by activating natural killer cells (NK) or redirecting a subject's immune response from a Th2 to a Th1 response by inducing monocytic and other cells to produce Th1 cytokines. The oligo(s) containing at least one unmethylated CpG can be used for treating and/or preventing respiratory and pulmonary diseases including bronchoconstriction, impaired airways, decreased lung surfactant, asthma, rhinitis, acute respiratory distress syndrome (ARDS), infantile or maternal RDS, chronic obstructive pulmonary disease (COPD), allergies, impeded respiration, lung pain, cystic fibrosis (CF), infectious diseases, cancers such as leukemias, lung and colon cancer, and the like, and diseases whose secondary effects afflict the lungs. A "CpG" or "CpG motif" refers to nucleotides having a cytosine followed by a guanine linked by a phosphate bond. The term "methylated CpG" refers to the methylation of the cytosine on the pyrimidine ring, usually occurring the 5-position of the pyrimidine ring. The term "unmethylated CpG" refers to the absence of methylation of the cytosine on the pyrimidine ring. Methylation, partial removal, or removal of an unmethylated CpG motif in an oligo(s) is believed to reduce its effect. Methylation or removal of all unmethylated CpG motifs in an oligo(s) substantially reduces its effect. The effect of methylation or removal of a CpG motif is "substantial" if the effect is similar to that of an oligonucleotide that does not contain a CpG motif. Preferably the CpG oligonucleotide is in the range of about 8 to 30 bases in size. The oligo(s) can be synthesized de novo using any of a number of procedures well known in the art. For example, the b-cyanoethyl phosphoramidite method (Beaucage, S. L., and Caruthers, M. H., Tet. Let. 22:1859, 1981); nucleoside H-phosphonate method (Garegg et al., Tet. Let. 27:4051-4054, 1986; Froehler et al., Nucl. Acid. Res. 14:5399-5407, 1986; Garegg et al., Tet. Let. 27:4055-4058, 1986; Gaffney et al., Tet. Let. 29:2619-2622, 1988). These chemistries can be performed by a variety of automated oligonucleotide synthesizers available in the market. Alternatively, CpG dinucleotides can be produced on a large scale in plasmids, (see Sambrook, T., et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor laboratory Press, New York, 1989) which after being administered to a subject are degraded into an oligo(s). An oligo(s) can be prepared from existing nucleic acid sequences (e.g., genomic or cDNA) using known techniques, such as those employing restriction enzymes, exonucleases or endonucleases. The exogenously administered agents of the invention decrease the levels of mRNA and protein encoded by the target gene and/or cause changes in the growth characteristics or shapes of the thus treated cells. See, Milligan et al. (1993); Helene, C. and Toulme, J. Biochim. Biophys. Acta 1049, 99-125 (1990); Cohen, J. S. D., Ed., Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression; CRC Press: Boca Raton, FL (1987), the relevant portion of which is hereby incorporated in its entirety by reference.

The treatment of this invention enhances the effects of the oligonucleotide and the anti-inflammatory steroid(s) and/or ubiquinone(s) by combining them, either simultaneously, sequentially or separately, for reducing or depleting levels of, or reducing sensitivity to, adenosine, reducing levels of receptor(s), producing bronchodilation, or for increasing levels of ubiquinone or lung surfactant in a subject's tissue (s), or treating bronchoconstriction, lung inflammation or allergies or a respiratory or lung disease or condition, and/or for alleviating bronchoconstriction or lung inflammation or allergy(ies), or ubiquinone or lung surfactant depletion or hyposecretion, in a subject. When administered in combination, the dose of the oligonucleotide or the steroid(s) or ubiquinone(s) may be decreased since they potentiate each other's effect. These agents may be administered before, simultaneously with, and/or after each other's administration. Accordingly, the details of administration of the effect enhancer including its amount, route, formulation, method, target organ and/or tissue may be determined as described throughout this specification. Similarly, other therapeutic or bioactive agents may be employed in accordance with this invention. Kits comprising the various agents described above are also part of this invention.

As used herein, "anti-sense oligonucleotide or anti-sense oligo" is generally a short sequence of synthetic nucleotide that hybridizes to any segment of a mRNA encoding a targeted protein under appropriate hybridization conditions and which, upon hybridization, causes a decrease in gene expression of the targeted protein. The terms "desAdenosine" (desA), "des-thymidine" (desT) and "des-uridine" (desU) refer to oligonucleotides substantially

lacking either adenosine (desA) or thymidine (desT) (uracil (desU)). In some instances, the desA or desT (desU) sequences are naturally occurring, and in others they may result from substitution of an undesirable nucleotide (A) by another lacking its undesirable activity, such as acting as an agonist or having a triggering effect at the adenosine A receptor(s). In the present context, the substitution is generally accomplished by substitution of A with a "universal or alternative base", presently known in the art or to be ascertained at a later time. As used herein, the terms "prevent", "preventing", "treat" or "treating" refer to a preventative, prophylactic, maintenance, or therapeutic treatment which decreases the likelihood that the subject administered such treatment will manifest symptoms associated with adenosine receptor stimulation. The term "down-regulate" refers to inducing a decrease in production, secretion or availability and, thus, a decrease in concentration, of intracellular target product, be it a receptor, e. g. adenosine A<sub>1</sub>, A<sub>2b</sub>, A<sub>3</sub>, bradykinin 2B, GATA-3, or other receptors, or produce a stimulatory effect on a receptor such as the adenosine A<sub>2a</sub> receptor. The present technology relies on the design of anti-sense oligos targeted to genes and mRNAs associated with ailments involving nasal and lung airway(s) (respiratory tract) pathology(ies), and on their modification to reduce the potential occurrence of undesirable side effects caused by their release of adenosine upon breakdown, while preserving their activity and efficacy for their intended purpose. In this manner, the inventor targets a specific gene to design one or more anti-sense single or double stranded DNA or RNA oligonucleotide(s) (oligos) that selectively bind(s) to the corresponding gene or mRNA, and then reduces, if necessary, their content of adenosine via substitution with an alternative or a universal base, or an adenosine analog incapable of significantly, or having substantially reduced ability for, activating or antagonizing adenosine A<sub>1</sub>, A<sub>2b</sub> or A<sub>3</sub> receptors or which may act as an agonist at the adenosine A<sub>2a</sub> receptor. Any number of adenosines present may be substituted by an alternative and/or universal base, such as heteroaromatic bases, which binds to a thymidine or uridine base but has less than about 0.3 of the adenosine base agonist or antagonist activity at the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> and A<sub>3</sub> receptors. Based on his prior experience in the field, the inventor reasoned that in addition to "downregulating" specific genes, he could increase the effect of the agent(s) administered by either selecting segments of RNA that are devoid, or have a low content, of thymidine (T) or uridine (U), or alternatively, substitute one or more adenosine(s) present in the designed oligonucleotide(s) with other nucleotide bases, so called universal bases, which bind to thymidine but lack the ability to activate adenosine receptors and otherwise exercise the constricting effect of adenosine in the lungs, etc. Given that adenosine (A) is a nucleotide base complementary to thymidine (T) or uridine (U), wherein when a U appears in the RNA, the anti-sense oligo will have an A at the same position.

In one aspect of this invention, the anti-sense oligonucleotide has a sequence which specifically binds to a portion or segment of a mRNA molecule which encodes or regulates the production of a protein associated with impeded breathing, allergy(ies), lung inflammation, depletion of lung surfactant or lowering of lung surfactant, airway obstruction, bronchitis, and the like. One effect of this binding is to reduce or even prevent the translation of the corresponding mRNA and, thereby, reduce the available amount of target protein in the subject's lung. In one preferred embodiment of this invention, the phosphodiester residues of the anti-sense oligonucleotide are modified or substituted. Chemical analogs of oligonucleotides with modified or substituted phosphodiester residues, e.g., to the methylphosphonate, the phosphotriester, the phosphorothioate, the phosphorodithioate, or the phosphoramidate, 2' methoxy ethyl and similar modifications, which increase the in vivo stability of the oligonucleotide are particularly preferred. The naturally occurring phosphodiester linkages of oligonucleotides are susceptible to some degree of degradation by cellular nucleases. Many of the residues proposed herein, on the contrary, are highly resistant to nuclease degradation. See, Milligan et al.; Cohen, J. S. D., *supra*. In another preferred embodiment of the invention, the oligonucleotides may be protected from degradation by adding a "3'-end cap" by which nuclease-resistant linkages are substituted for phosphodiester linkages at the 3' end of the oligonucleotide. See, Tidd, D. M. and Warenus, H.M., *Be. J. Cancer* 60: 343-350 (1989); Shaw, J.P. et al., *Nucleic Acids Res.* 19: 747-750 (1991), the relevant section of which are incorporated in their entireties herein by reference. Phosphoramidates, phosphorothioates, and methylphosphonate linkages all function adequately in this manner for the purposes of this invention, as do 2' modifications, such as 2' methoxy ethyl, and the like. The more extensive the modification of the phosphodiester backbone the more stable the resulting agent, and in many instances the higher their RNA affinity and cellular permeation. See, Milligan, et al., *supra*. In addition, a plurality of substitutions to the carbohydrate ring are also known to improve stability of nucleic acids. Thus, the number of residues which may be modified or substituted will vary depending on the need, target, and route of administration, and may be from 1 to all the residues, to any number in between. Many different methods for replacing the entire phosphodiester backbone with



novel linkages are known. See, Millikan et al, supra. Preferred backbone analogue residues include phosphoramidate, phosphorothioate, methylphosphonate, phosphotriester, phosphotriester, thioformacetal, phosphorodithioate, phosphoramidate, formacetal, triformacetal, thioether, carbamate, boranophosphate, 3'-thioformacetal, 5'-thioether, carbonate, C<sub>5</sub>-substituted nucleotides, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, 2'-O methyl, sulfoxide, sulfide, hydroxylamine, methylene(methylimino) (MMI), methoxymethyl (MOM), and methoxyethyl (MOE), and methyleneoxy(methylimino) (MOMI) residues, and combinations thereof. Phosphorothioate and methylphosphonate-modified oligonucleotides are particularly preferred due to their availability through automated oligonucleotide synthesis. See, Millikan et al, supra. Where appropriate, the agent of this invention may be administered in the form of their pharmaceutically acceptable salts, or as a mixture of the anti-sense oligonucleotide and its salt. In another embodiment of this invention, a mixture of different anti-sense oligonucleotides or their pharmaceutically acceptable salts is administered. A single agent of this invention has the capacity to attenuate the expression of a target mRNA and/or various agents to enhance or attenuate the activity of a pathway. By means of example, the present method may be practiced by identifying all possible deoxyribonucleotide segments which are low in thymidine (T), ribonucleotides that are low in uridine (U), or deoxynucleotide segments low in adenosine (A) of about 7 or more mononucleotides, preferably up to about 60 mononucleotides, more preferably about 10 to about 36 mononucleotides, and still more preferably about 12 to about 21 mononucleotides, in a target mRNA or a gene, respectively. This may be attained by searching for nucleotide segments within a target sequence which are low in, or lack thymidine (DNA) or uridine (RNA), a nucleotide which is complementary to adenosine, or that are low in adenosine (gene), that are 7 or more nucleotides long. In most cases, this search typically results in about 10 to 30 such sequences, i.e. naturally lacking or having less than about 40% adenosine, anti-sense oligonucleotides of varying lengths for a typical target mRNA of average length, i.e., about 1800 nucleotides long. Those with high content of T, U or A, respectively, may be fixed by substitution of a universal base for one or more As. The agent(s) of this invention may be of any suitable length, including but not limited to, about 7 to about 60 nucleotides long, preferably about 12 to about 45, more preferably up to about 30 nucleotides long, and still more preferably up to about 21, although they may be of other lengths as well, depending on the particular target and the mode of delivery. The agent(s) of the invention may be directed to any and all segments of a target RNA. One preferred group of agent(s) includes those directed to an mRNA region containing a junction between an intron and an exon. Where the agent is directed to an intron/exon junction, it may either entirely overlie the junction or it may be sufficiently close to the junction to inhibit the splicing-out of the intervening exon during processing of precursor mRNA to mature mRNA, e.g. with the 3' or 5' terminus of the anti-sense oligonucleotide being positioned within about, for example, within about 2 to 10, preferably about 3 to 5, nucleotide of the intron/exon junction. Also preferred are anti-sense oligonucleotides which overlap the initiation codon, and those near the 5' and 3' termini of the coding region. The flanking regions of the exons may also be targeted as well as the spliced segments in the precursor mRNAs. The mRNA sequences of the adenosine receptors and of many other targets are derived from the DNA base sequence of the gene expressing either receptors, e. g. the adenosine receptors, the enzymes, factors, or other targets associated with airway disease. For example, the sequence of the genomic human A<sub>1</sub> adenosine receptor is known and is disclosed in U.S. Patent No. 5,320,963 to Stiles, G., et al. The A<sub>3</sub> adenosine receptor has been cloned, sequenced and expressed in rat (see, Zhou, F., et al., P.N.A.S. (USA) 89: 7432 (1992)) and human (see, Jacobson, M. A., et al., U.K. Patent Application No. 9304582.1 (1993)). The sequence of the adenosine A<sub>2b</sub> receptor gene is also known. See, Salvatore, C. A., Luneau, C. J., Johnson, R. G. and Jacobson, M., Genomics (1995), the relevant portion of which is hereby incorporated in its entirety by reference. The sequences of many of the remaining exemplary target genes are also known. See, GenBank, NIH. The sequences of those genes whose sequences are not yet available may be obtained by isolating the target segments applying technology known in the art. Once the sequence of the gene, its RNA and/or the protein are known, an anti-sense oligonucleotides may be produced according to this invention as described above to reduce the production of the targeted protein in accordance with standard techniques. The sequences for the adenosine A<sub>2a</sub> bradykinin, and other genes as well as methods for preparation of oligonucleotides are also known as those of many other target genes and mRNAs for which this invention is suitable. Thus, anti-sense oligonucleotides that downregulate the production of target sequences associated with airway disease, including the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, A<sub>3</sub>, bradykinin, GATA-3, COX-2, and many other receptors, may be produced in accordance with standard techniques. Examples of diseases and conditions which are suitably treated by the present method are diseases and conditions, including Acute Respiratory Distress Syndrome (ARDS), asthma, adenosine administration e.g. in the



treatment of SupraVentricular Tachycardia (SVT) and other arrhythmias, and in stress tests to hyper-sensitized individuals, ischemia, renal damage or failure induced by certain drugs, infantile respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, and cancers such as leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer.

The adenosine receptors discussed above are mere examples of the high power of the inventor's technology. In fact, a large number of genes may be targeted in a similar manner by the present agent(s), to reduce or down-regulate protein expression. This targeting may be attained by selecting a single target, or multiple targets. In the latter case, the oligos targeted to different sequences may be mixed for their administration or they may be multiple targeted anti-sense oligos (MTAs) in accordance with one embodiment of this invention; that is, the MTA sequence binds to more than one target polynucleotide, be it DNA or RNA. By means of example, if the target disease or condition is one associated with impeded or reduced breathing, bronchoconstriction, chronic bronchitis, pulmonary bronchoconstriction and/or hypertension, chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, allergy, asthma, cystic fibrosis, respiratory distress syndrome, cancers, which either directly or by metastasis afflict the lung, the present method may be applied to a list of potential target mRNAs, which includes the targets listed in Table 1 and Table 2 below, among others. The anti-sense agent(s) of the invention have a low A content to prevent its liberation upon in vivo degradation of the agent(s). For example, if the system is the pulmonary or respiratory system, a large number of genes is involved in different functions, including those listed in Table 1 below.

**Table 1: Pulmonary and Inflammatory Targets**

	NFκB Transcription Factor	Interleukin-8 Receptor (IL-8 R)
	Interleukin-5 Receptor (IL-5R)	Interleukin-4 Receptor (IL-4R)
25	Interleukin-3 Receptor (IL-3R)	Interleukin-1β (IL-1β)
	Interleukin-1β Receptor (IL-1βR)	Eotaxin
	Tryptase	Major Basic Protein
	β2-adrenergic Receptor Kinase	Endothelin Receptor A
	Endothelin Receptor B	Preproendothelin
30	Bradykinin B2 Receptor (B2BR)	IgE (High Affinity Receptor)
	Interleukin-1 (IL-1)	Interleukin 1 Receptor (IL-1 R)
	Interleukin-9 (IL-9)	Interleukin-9 Receptor (IL-9 R)
	Interleukin-11 (IL-11)	Interleukin-11 Receptor (IL-11 R)
	Inducible Nitric Oxide Synthase	Cyclooxygenase (COX)
35	Intracellular Adhesion Molecule 1 (ICAM-1)	Vascular Cellular Adhesion Molecule (VCAM)
	Substance P	Endothelial Leukocyte Adhesion Molecule Endothelin ETA Receptor (ELAM-1)
	Rantes	GM-CSF, Endothelin-1
	Cyclooxygenase-2 (COX-2)	Neutrophil Chemotactic Factor
40	Monocyte Activating Factor	Defensin 1,2,3
	Neutrophil Elastase	Platelet Activating Factor
	Muscarinic Acetylcholine Receptors	5-lipoxygenase
	Tumor Necrosis Factor α	Substance P
	Phosphodiesterase IV	Histamine Receptor
45	Substance P Receptor	CCR-1 CC Chemokine Receptor
	Chymase	Interleukin-4 (IL-4)
	Interleukin-2 (IL-2)	Interleukin-5 (IL-5)
	Interleukin-12 (IL-12)	Interleukin-7 (IL-7)
	Interleukin-6 (IL-6)	Interleukin-12 Receptor (IL-12R)
50	Interleukin-8 (IL-8)	Interleukin-1 (IL-1)
	Interleukin-7 Receptor (IL-7R)	

	Interleukin-14 Receptor (IL-14R)	Interleukin-14
	CCR-2 CC Chemokine Receptor	CCR-3 CC Chemokine Receptor
	CCR-4 CC Chemokine Receptor	CCR-5 CC Chemokine Receptor
	Prostanoid Receptors	GATA-3 Transcription Factor
5	Neutrophil Adherence Receptor	MAP Kinase
	Interleukin-15 (IL-15)	Interleukin-15 Receptor (IL-15R)
	Interleukin-11 (IL-11)	Interleukin-11 Receptor (IL-11R)
	NFAT Transcription Factors	STAT 4
	MIP-1 $\alpha$	MCP-2
10	MCP-3	MCP-4
	Cyclophilin (A, B, etc.)	Phospholipase A2
	Basic Fibroblast Growth Factor	Metalloproteinase
	CSBP/p38 MAP Kinase	Tryptase Receptor
	PDG2	Interleukin-3 (IL-3)
15	Interleukin-10 (IL-10)	Cyclosporin A - Binding Protein
	FK506-Binding Protein	$\alpha 4\beta 1$ Selectin
	Fibronectin	$\alpha 4\beta 7$ Selectin
	cMad CAM-1	LFA-1 (CD11a/CD18)
	PECAM-1	LFA-1 Selectin
20	C3bi	PSGL-1
	E-Selectin	P-Selectin
	CD-34	L-Selectin
	p150,95	Mac-1 (CD11b/CD18)
	Fucosyl transferase	VLA-4
25	STAT-1	STAT-2
	CD-18/CD11a	CD11b/CD18
	ICAM2 and ICAM3	C5a
	CCR3 (Eotaxin Receptor)	CCR1, CCR2, CCR4, CCR5
	LTB-4	AP-1 Transcription Factor
30	Protein kinase C	Cysteinyl Leukotriene Receptor
	Tachykinnen Receptors (tach R)	I $\kappa$ B Kinase 1 & 2
	Interleukin-2 Receptor (IL-2R)	(e.g., Substance P, NK-1 & NK-3 Receptors)
	STAT 6	c-mas
	NF-Interleukin-6 (NF-IL-6)	Interleukin-10 Receptor (IL-10R)
35	Interleukin-3 (IL-3)	Interleukin-2 Receptor (IL-2R)
	Interleukin-13 (IL-13)	Interleukin-12 Receptor (IL-12R)
	Interleukin-14 (IL-14)	Interleukin-6 Receptor (IL-6R)
	Interleukin-16 (IL-16)	Interleukin-13 Receptor (IL-13R)
	Medullasin	Interleukin-16 Receptor (IL-16R)
40	Adenosine A <sub>1</sub> Receptor (A <sub>1</sub> R)	Tryptase-I
	Adenosine A <sub>2b</sub> Receptor (A <sub>2b</sub> R)	Adenosine A <sub>3</sub> Receptor (A <sub>3</sub> R)
	$\beta$ Tryptase	STAT-3
	Adenosine A <sub>2a</sub> Receptor (A <sub>2a</sub> R)	IgE Receptor $\beta$ Subunit (IgE R $\beta$ )
	Fc-epsilon receptor CD23 antigen	IgE Receptor $\alpha$ Subunit (IgE R $\alpha$ )
45	IgE Receptor Fc Epsilon Receptor (IgERFc $\xi$ R)	Substance P Receptor
	Histidine decarboxylase	Tryptase-1
	Prostaglandin D Synthase	Eosinophil Cationic Protein
	Eosinophil Derived Neurotoxin	Eosinophil Peroxidase
	Endothelial Nitric Oxide Synthase	Endothelial Monocyte Activating Factor
50	Neutrophil Oxidase Factor	Cathepsin G
	Macrophage Inflammatory Protein-1-	Interleukin-8 Receptor $\alpha$ Subunit (IL-8 R $\alpha$ )
	Alpha/Rantes Receptor	Endothelin Receptor ET-B

- |    |  |  |
|----|--|--|
|    | H2A histone family, member N   | Tubulin, beta polypeptide                                    |
|    | ELL gene (11-19 lysine-rich leukemia gene)   | 7-dehydrocholesterol reductase                               |
|    | ADP-ribosylation factor-like 7   | Karyopherin alpha 2 (RAG cohort 1, importin alpha 1)         |
|    | EST (AI038433)   | EST (AI122689)   |
| 5  | EST (AI092623)   | ESTs (AI095492)  |
|    | ESTs (AI138216)  | ESTs (AI128305)  |
|    | ESTs (AI125228)  | ESTs (AI041482)  |
|    | ESTs (AI051839)  | Homo sapiens mRNA; cDNA DKFZp434A1716                        |
|    | ESTs (AI096522)  | ESTs (AI122807)  |
| 10 | ESTs (AI041212)  | EST (AI125651)   |
|    | Enolase 1, (alpha)   | EST (AI024215)   |
|    | EST (AI034360)   | Homo sapiens mRNA; cDNA DKFZp564H0764                        |
|    | Homo sapiens mRNA for KIAA1363 protein, partial cds  |  |
|    | Potassium voltage-gated channel, shaker-related subfamily, beta member 2                             |  |
| 15 | ER-associated DNAJ; ER-associated Hsp40 co-chaperone; hDj9; ERj3                                     |  |
|    | ESTs, Weakly similar to p38 protein [H.sapiens] (AA906703)   |  |
|    | CGI-142  | ESTs (AA463249)  |
|    | Homo sapiens clone 25058 mRNA sequence   | ESTs (R49144)  |
|    | Squamous cell carcinoma antigen 1  | ESTs (AA425700)  |
| 20 | Myosin X   | ESTs (AA459692)  |
|    | Epithelial protein lost in neoplasm beta   | CD44 antigen (homing function and Indian blood group system) |
|    | Coagulation factor III (thromboplastin, tissue factor)   |  |
|    | ESTs (AA090635)  | Adducin 1 (alpha)  |
|    | 5' Nucleotidase (CD73)   |  |
| 25 | ESTs, Moderately similar to semaphorin C [M.musculus] (AA293300)                                     |  |
|    | ESTs (AA278764)  | ESTs (AA678160)  |
|    | Calmodulin 2 (phosphorylase kinase, delta)   | ESTs (R42770)  |
|    | Chloride intracellular channel 1   | High-mobility group (nonhistone chromosomal) protein 17      |
|    | Ubiquitin carrier protein  | Tubulin, alpha 1 (testis specific)                           |
| 30 | Transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)                      |  |
|    | Sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican)                               |  |
|    | Proteasome (prosome, macropain) 26S subunit, non-ATPase, 2   |  |
|    | Tubulin, beta polypeptide  | Filamin B, beta (actin-binding protein-278)                  |
|    | Stanniocalcin  |  |
| 35 | Low density lipoprotein receptor (familial hypercholesterolemia)                                     |  |
|    | Plectin 1, intermediate filament binding protein, 500kD  |  |
|    | S100 calcium-binding protein A2  | Immediate early response 3                                   |
|    | Calpain, large polypeptide L2  | Pleckstrin homology-like domain, family A, member 1          |
|    | Melanoma adhesion molecule   |  |
| 40 | CD44 antigen (homing function and Indian blood group system)   |  |
|    | Programmed cell death 5  | Hexokinase 1   |
|    | Vascular endothelial growth factor   | Integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor) |
|    | Calumenin  | Syntaxin 11  |
|    | Diphtheria toxin receptor (heparin-binding epidermal growth factor-like growth factor)               |  |
| 45 | Fnl4 for type I transmembrane protein  | Nef-associated factor 1                                      |
|    | High-mobility group (nonhistone chromosomal) protein isoforms I and Y                                |  |
|    | Catechol-O-methyltransferase   | C-terminal binding protein 1                                 |
|    | Collagen, type XVII, alpha 1   | ESTs (N58473)  |
|    | Farnesyl-diphosphate farnesyltransferase 1   | RNA helicase-related protein                                 |
| 50 | Interferon stimulated gene (20kD)  |  |
|    | Steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1) |  |
|    | Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)                |  |

Laminin, alpha 3 (nicein (150kD), kalinin (165kD), BM600 (150kD), epilegrin)  
 Collagen, type XVII, alpha 1 Keratin 18  
 Heparan sulfate (glucosamine) 3-O-sulfotransferase 1  
 Tubulin, alpha 2 Adenylyl cyclase-associated protein  
 5 Forkhead box D1 Cathepsin C  
 ESTs, Highly similar to AF151802\_1 CGI-44 protein [H.sapiens] (T74688)  
 Ribonucleotide reductase M2 polypeptide  
 Laminin, gamma 2 (nicein (100kD), kalinin (105kD), BM600 (100kD), Herlitz junctional epidermolysis bullosa))  
 Homo sapiens mRNA; cDNA DKFZp586P1622 (from clone DKFZp586P1622)  
 10 ESTs, Weakly similar to /prediction (AA284245)  
Lactate dehydrogenase A

Note that in the parantheses after "EST(s)" is GENABNK ACESSION NO.

These genes, and others, are involved in the normal functioning of respiration as well as in diseases associated with respiratory pathologies, including cystic fibrosis, asthma, pulmonary hypertension and  
 15 vasoconstriction, chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, chronic bronchitis, respiratory distress syndrome (ARDS), allergic rhinitis, lung cancer and lung metastatic cancers and other airway diseases, including those with inflammatory response.

Anti-sense oligos to the target receptors, e. g. the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and A<sub>3</sub> receptors, CCR3 (chemokine receptors), bradykinin 2B, VCAM (vascular cell adhesion molecule), and eosinophil receptors, among  
 20 others, have been shown to be effective in down-regulating the expression of their genes. Some of these act to alleviate the symptoms or reduce respiratory ailments and/or inflammation, for example, by "down regulation" of the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and/or A<sub>3</sub> receptors and CCR3, bradykinin 2B, VCAM (vascular cell adhesion molecule) and eosinophil receptors. These agents may be utilized by the present method alone or in conjunction with anti-sense oligos targeted to other genes to validate pathway and/or networks in which they are involved. For better  
 25 results, the oligos are preferably administered directly into the respiratory system, e.g., by inhalation or other means, of the experimental animal, so that they may reach the lungs without widespread systemic dissemination. This permits the use of low agent doses as compared with those administered systemically or by other generalized routes and, consequently, reduces the number and degree of undesirable side effects resulting from the agent's widespread distribution in the body. The agent(s) of this invention has (have) been shown to reduce the amount of receptor protein expressed by the tissue. These agents, thus, rather than merely interacting with their targets, e.g. a receptor, lower the number of target proteins that other drugs may interact with. In this manner, the present agent(s) afford(s) extremely high efficacy with low toxicity. Anti-sense oligonucleotides to the A<sub>1</sub>, A<sub>2b</sub>, A<sub>3</sub>, bradykinin B2, GATA-3, VCAM (vascular cell adhesion molecule), eosinophil receptors, and COX-2 receptors, among others, have been  
 30 shown to be effective in the down-regulation of the respective receptor proteins in the cell. One novel feature of this treatment, as compared to traditional treatments for adenosine-mediated bronchoconstriction, is that administration is direct to the lungs, or in situ to other tissues, organs or systems of the body. Additionally, a receptor protein itself is reduced in amount, rather than merely interacting with a drug, and toxicity is reduced. Other proteins that may be targeted with anti-sense agents for the treatment of lung conditions include, but are not limited to: CCR3 (chemokine) receptors, human A<sub>2a</sub> adenosine receptor, human A<sub>2b</sub> adenosine receptor, human IgE receptor  $\beta$ , human  
 40 Fc-epsilon receptor CD23 antigen, human histidine decarboxylase, human beta tryptase, human tryptase-I, human prostaglandin D synthase, human cyclooxygenase-2, human eosinophil cationic protein, human eosinophil derived neurotoxin, human eosinophil peroxidase, human intercellular adhesion molecule-1 (ICAM-1), human vascular cell adhesion molecule-1 (VCAM-1), human endothelial leukocyte adhesion molecule-1 (ELAM-1), human P selectin, human endothelial monocyte activating factor, human IL-3, human IL-4, human IL-5, human IL-6, human IL-8,  
 45 human monocyte-derived neutrophil chemotactic factor, human neutrophil elastase, human neutrophil oxidase factor, human cathepsin G, human defensin 1, human defensin 3, human macrophage inflammatory protein-1-alpha, human muscarinic acetylcholine receptor HM3, human fibronectin, human GM-CSF, human tumor necrosis factor  $\alpha$ , human leukotriene C4 synthase, human major basic protein, and human endothelin 1. Although not intended to be exclusive, a more extensive list of genes and sequences are provided below. Some of these act to alleviate the  
 50 symptoms or reduce respiratory ailments and/or inflammation, for example, by "down regulation" of the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and/or A<sub>3</sub> receptors and CCR3, bradykinin 2B, VCAM (vascular cell adhesion molecule) and eosinophil receptors. These agents are preferably administered directly into the respiratory system, e.g., by

inhalation or other means, so that they may reach the lungs without widespread systemic dissemination. This permits the use of substantially lower doses of the agent of the invention as compared with those administered by the prior art, systemically or by other generalized routes and, consequently, reduce undesirable side effects resulting from the agent's widespread distribution in the body. The agent(s) of this invention has (have) been shown to reduce the amount of receptor protein expressed by the tissue. These agents, thus, rather than merely interacting with their targets, e.g. a receptor, lower the number of target proteins that other drugs may interact with. In this manner, the present agent(s) afford(s) extremely high efficacy with low toxicity. In these latter targets, and in target genes in general, it is particularly imperative to eliminate or reduce the adenosine content of the corresponding anti-sense oligonucleotide to prevent their breakdown products from liberating adenosine.

As used herein, the term "treat" or "treating" refers to a treatment which decreases the likelihood that the subject administered such treatment will manifest symptoms of the respiratory, lung or other diseases. The term "downregulate" refers to inducing a decrease in production, secretion or availability (and thus a decrease in concentration) of the targeted intracellular protein. The present invention is concerned primarily with the treatment of human subjects. However, the agents and methods disclosed here may also be employed for veterinary purposes, such as is the case in the treatment of other mammals, such as cattle, horses, wild animals, zoo animals, and domestic animals, e. g. dogs and cats. Targeted proteins may be prokaryotic or eukaryotic or mammalian and more preferably of the same species as the subject being treated. In general, "anti-sense" refers to the use of small, synthetic oligonucleotides, resembling single-stranded DNA, to inhibit gene expression by inhibiting the function of the target messenger RNA (mRNA). Milligan, J. F. et al., *J. Med. Chem.* 36(14), 1923-1937 (1993). In the present invention, inhibition of gene expression of the A<sub>1</sub> or A<sub>3</sub> adenosine receptor is desired. Gene expression is inhibited through hybridization to coding (sense) sequences in a specific messenger RNA (mRNA) target by hydrogen bonding according to Watson-Crick base pairing rules. The mechanism of anti-sense inhibition is that the exogenously applied oligonucleotides decrease the mRNA and protein levels of the target gene or cause changes in the growth characteristics or shapes of the cells. Id. See, also Helene, C. and Toulme, J., *Biochim. Biophys. Acta* 1049, 99-125 (1990); Cohen, J. S. D., Ed., *Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression*; CRC Press: Boca Raton, FL (1987). As used herein, "anti-sense oligonucleotide" is defined as a short sequence of synthetic nucleotide that (1) hybridizes to any sense or anti-sense sequence in a mRNA or DNA which codes for the targeted protein or their double stranded counterparts, according to in vitro or in vivo hybridization conditions, described below, and (2) upon hybridization causes a decrease in gene expression of the target, e.g. adenosine or other receptor(s). The receptors discussed above are mere examples of the high power of the present technology. In fact, a large number of genes and mRNAs may be targeted in a similar manner by the present methods, to significantly down-regulate or obliterate their protein expression and observe any changes wrought to one or more functions within a system, e.g. the respiratory system and other lung disease associated targets. By means of example, in the respiratory system, the targets may be associated with difficulties of breathing, bronchoconstriction, inflammation, allergic rhinitis, chronic bronchitis, surfactant depletion, and others associated with diseases and conditions such as chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, inhalation burns, Acute Respiratory Distress Syndrome (ARDS), cystic fibrosis, pulmonary fibrosis, radiation pneumonitis, tonsillitis, emphysema, dental pain, oral inflammation, joint pain, esophagitis, cancers afflicting the respiratory system either directly such as lung cancer, esophageal cancer, and the like, or indirectly by means of metastases, among others. These functions are of great interest because of their association with respiratory dysfunction, as is the case in asthma, allergies, allergic rhinitis, pulmonary bronchoconstriction and hypertension, chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary infections, allergy, asthma, cystic fibrosis (CF), Acute Respiratory Distress Syndrome (ARDS) as well as infantile and pregnancy-related RDS, cancer, etc., which either directly or by metastasis afflict the lung, the present anti-sense oligonucleotides may be directed to a list of target mRNAs, which includes the targets listed in Table 1 above, among others.

Oligonucleotides, whether DNA or RNA, may be synthesized by methods known in the art that need not be further described here. The low adenosine oligos of this invention may be obtained by first selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C and/or having a specific type and/or extent of activity, and then obtaining a first oligonucleotide 4 to 60 nucleotides long which comprises the selected fragment and has a thymidine (T) or uridine (U) nucleic acid content of up to and including about 15%, preferably, about 12%, about 10%, about 7%, about 5%, about 3%, about 1%, and more

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15  
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25 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are independently H, alkyl, alkenyl or alkynyl and R<sup>3</sup> is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH<sub>2</sub>-alkylamino-ketoxyalkyloxy-aryl, or mono or dialkylaminoalkyl-N-alkylamino-SO<sub>2</sub>aryl, and R<sup>4</sup> and R<sup>5</sup> are independently R<sup>1</sup> and together are R<sup>3</sup>, and the pyrimidines and purines optionally comprise theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline or xantine, among  
30 others. Similar modifications in the sugar are also embodiments of this invention. Reduced adenosine content of the anti-sense oligos corresponding to the thymidines (T) present in the target DNA or uridines (U) in the target RNA serves to prevent the breakdown of the oligos into products that free adenosine into the system, e.g. the lung, brain, heart, kidney, etc., tissue environment and, thereby, to prevent any unwanted effects due to it. By means of example, the NfκB transcription factor may be selected as a target, and its mRNA or DNA searched for low  
35 thymidine (T), low uridine (U) or desthymidine (desT) or desuridine (desU) fragments. Only desU and desT segments of the mRNA or DNA are selected which, in turn, will produce desA anti-sense as their complementary strand. When a number of DNA or RNA that are desT or desU segments are found, the sequence of the anti-sense segments may be deduced. Typically, about 10 to 30 and even larger numbers of desA anti-sense sequences may be obtained. These anti-sense sequences may include some or all desA anti-sense oligonucleotide sequences

corresponding to desU or desT segments of the mRNA or DNA of the target, such as anyone of those shown in Table 1 above, in Table 2 below, and others associated with functions of the brain, cardiovascular and renal systems, and many others. For each of the original desA anti-sense oligonucleotide sequences corresponding to the target gene, e.g. the NF $\kappa$ B transcription factor, typically about 10 to 30 sequences may be found within the target gene or RNA which have a low content of thymidine (DNA) or uridine (RNA). In accordance with this invention, the selected fragment sequences may also contain a small number of thymidine (DNA) or uridine (RNA) nucleotides within the secondary or tertiary or quaternary sequences. In some cases, a large adenosine content may suffice to render the anti-sense oligonucleotide less active or even inactive against the target. In accordance with this invention, these so called "non-fully desA" sequences may preferably have a content of adenosine of less than about 15%, about 12%, about 10%, about 7%, about 5%, and about 2% adenosine. Most preferred is no adenosine content (0%). In some instances, however, a higher content of adenosine is acceptable and the oligonucleotides still fail to show detrimental "adenosine activity". A particular important embodiment is that where the adenosine nucleotide is "fixed" or replaced by a "universal or alternative" base that may base-pair with similar or equal affinity to two or more of the four nucleotides present in natural DNA: A, G, C, and T.

A universal or alternative base is defined in this patent as any compound, more commonly an adenosine analogue, which has substantial capacity to hybridize to thymidine or uridine, while at the same time having reduced, or substantially lacking, ability to bind adenosine receptors or other molecules through which adenosine may exert an undesirable side effect in the experimental animal or in a cell system. Alternatively, adenosine analogs which completely fail to activate, or have significantly reduce ability for activating, adenosine receptors, such as the adenosine A<sub>1</sub>, A<sub>2b</sub> and/or A<sub>3</sub> receptors, most preferably A<sub>1</sub> receptors, and those that may even act as agonists of the adenosine A<sub>2b</sub> receptor, may be used. One example of a universal base is 2'-deoxyribofuranosyl-(5-nitroindole), and an artisan will know how to select others. This "fixing" step generates further novel sequences, different from those anti-sense to the ones found in nature, that permits the anti-sense oligonucleotide to bind, preferably equally well, with the target RNA. Other examples of universal or alternative bases are 2'-deoxyribosyl-(5-nitroindole). Other examples of universal bases are 3 - nitropyrrole - 2' - deoxynucleoside, 5 - nitro-indole, 2' - deoxyribosyl - (5 - nitroindole), 2'-deoxyribofuranosyl - (5-nitroindole), 2' - deoxyinosine, 2' - deoxynebularine, 6H, 8H-3,4-dihydropyrimido [ 4, 5 - c] oxazine - 7 - one and 2 - amino - 6 -methoxy aminopurine. In addition to the above, Universal bases which may be substituted for any other base although with somewhat reduced hybridization potential, include 3 - nitropyrrole - 2' - deoxynucleoside 2' - deoxyribofuranosyl - (5 - nitroindole), 2' - deoxyinosine and 2' - deoxynebularine (Glen Research, Sterling, VA). More specific mismatch repairs may be made using "P" nucleotide, 6H, 8H - 3, 4 - dihydropyrimido [4,5 - c] [1, 2] oxazin - 7 - one, which base pairs with either guanosine (G) or adenosine (A) and "K" nucleotide, 2 - amino - 6 - methoxyaminopurine, which base pairs with either cytidine (C) or thymidine (T)-uridine (U), among others. Others that are known in the art or will become available are also suitable. See, for example, Loakes, D. and Brown, D. M., Nucl. Acids Res. 22:4039-4043 (1994); Ohtsuka, E. et al., J. Biol. Chem.260(5):2605-2608 (1985); Lin, P.K.T. and Brown, D. M., Nucleic Acids Res. 20(19):5149-5152 (1992); Nichols, R. et al., Nature 369(6480): 492-493 (1994); Rahmon, M. S. and Humayun, N. Z., Mutation Research 377 (2): 263-8 (1997); Amosova, O., et al., Nucleic Acids Res. 25 (10): 1930-1934 (1997); Loakes D. & Brown, D. M., Nucleic Acids Res. 22 (20): 4039-4043 (1994), the entire sections relating to universal bases and their preparation and use in nucleic acid binding being incorporated herein by reference. When non-fully desT sequences are found in the naturally occurring target, they typically are selected so that about 1 to 3 universal base substitutions will suffice to obtain a 100% "desA" anti-sense oligonucleotide. Thus, the present method provides either anti-sense oligonucleotides to different targets which are low in, or devoid of, A content, as well as anti-sense oligonucleotides where one or more adenosine nucleotides, e. g. about 1 to 3, or more, may be "fixed" by replacement with a "universal" or "replacement" base. Universal bases are known in the art and need not be listed herein. An artisan will know which bases may act as universal bases, and replace them for A. Table 2 below provides a selected number of targets to which the agents of the invention are effectively applied. Others, however, may also be targeted.

**Table 2: Cancer Targets**

Transforming Oncogenes	Therapy Targets
ras	thymidylate synthetase
src	thymidylate synthetase

	myc	dihydrofolate reductase
	bcl-2	thymidine kinase
		deoxycytidine kinase
		ribonucleotide reductase
5	Angiogenesis factors	Adhesion Molecules
	Oncogenes	Folate Pathway Enzymes
	DNA repair genes	(One Carbon Pool)
		Telomerase
		HMG CoA Reductase
10		Farnesyl Transferase
		Glucose-6-Phosphate Transferase Akt2 (Bases 1-1715)
	Akt3 (1-1547)	
	Ampiregulin (1-1230))	
	Ap-2 (1-1391)	
15	Ap-2 Beta	
	Ap-2 Gamma	
	Sphingomyelinase	
	Beta-2-Adrenergic Receptor	
	Beta Catenin	
20	E2F-Related Transcription Factor	
	HM bFGF	
	B-cell translocation gene 1 (BTG1)	
	cyclin-dependent kinase 2 (CDK2)	
	cyclin-dependent kinase 2 (CDK2)	
25	cyclin-dependent kinase 3 (CDK3)	
	cyclin-dependent kinase 4 (CDK4)	
	cyclin-dependent kinase 5 (CDK5)	
	c-ets-1 proto-oncogene	
	checkpoint kinase Chk1 (CHK1)	
30	type IV collagenase	
	hepatocyte growth factor receptor (c-met)	
	<u>MYB proto-oncogene protein (MYB)</u>	

A group of preferred targets for the treatment of cancer are genes associated with any of different types of cancers, or those generally known to be associated with malignancies, whether they are regulatory or involved in the production of RNA and/or proteins. Examples are transforming oncogenes, including, but not limited to, ras, src, myc, and BCL-2, among others. Other targets are those to which present cancer chemotherapeutic agents are directed to, such as various enzymes, primarily, although not exclusively, thymidylate synthetase, dihydrofolate reductase, thymidine kinase, deoxycytidine kinase, ribonucleotide reductase, and the like. The present technology is particularly useful in the treatment of cancer ailments given that traditional cancer therapies are fraught with the unresolved problem of selectively killing cancer cells while preserving normal living cells from the devastating effects of treatments such as chemotherapy, radiotherapy, and the like. The present technology provides the ability of selectively attenuating or enhancing a desired pathway or target. This approach provides a significant advantage over standard treatments of cancer because it permits the selection of a pathway, including primary, secondary and possibly tertiary targets, which are not generally expressed simultaneously in normal cells. Thus, the present agent may be administered to a subject to cause a selective increase in toxicity within tumor cells that, for instance, express all three targets while normal cells that may express only one or two of the targets will be significantly less affected or even spared. A group of preferred targets for the treatment of cancers are genes associated with different types of cancers, or those generally known to be associated with malignancies, whether they are regulatory or involved in the production of RNA and/or proteins. Examples are transforming oncogenes, including, but not limited to, ras, src, myc, and BCL-2, among others. Other targets are those to which present cancer chemotherapeutic agents are directed to, such as various enzymes, primarily, although not exclusively, thymidylate synthetase, dihydrofolate



reductase, thymidine kinase, deoxycytidine kinase, ribonucleotide reductase, and the like.

In one embodiment, at least one of the genes or mRNAs to which the oligo of the invention is targeted encodes or is involved in the regulation of a protein such as transcription factors, stimulating and activating factors, intracellular and extracellular receptors and peptide transmitters in general, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific and non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) and peripheral nervous and non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensins, growth factors, vasoactive peptides and receptors, and binding proteins, among others; or the mRNA is corresponding to an oncogene and other genes associated with various diseases or conditions. Examples of target proteins are eotaxin, major basic protein, preproendothelin, eosinophil cationic protein, P-selectin, STAT 4, MIP-1 $\alpha$ , MCP-2, MCP-3, MCP-4, STAT 6, c-mas, NF-IL-6, cyclophilins, PDG2, cyclosporin A-binding protein, FK5-binding protein, fibronectin, LFA-1 (CD11a/CD18), PECAM-1, C3bi, PSGL-1, CD-34, substance P, p150,95, Mac-1 (CD11b/CD18), VLA-4, CD-18/CD11a, CD11b/CD18, C5a, CCR1, CCR2, CCR4, CCR5, and LTB-4, among others. Others are, however, suitable, as well. In another embodiment, at least one of the mRNAs to which the oligo is targeted encodes intracellular and extracellular receptors and peptide transmitters such as sympathomimetic receptors, parasympathetic receptors, GABA receptors, adenosine receptors, bradykinin receptors, insulin receptors, glucagon receptors, prostaglandin receptors, thyroid receptors, androgen receptors, anabolic receptors, estrogen receptors, progesterone receptors, receptors associated with the coagulation cascade, adenohipophyseal receptors, adenohipophyseal peptide transmitters, and histamine receptors (HisR), among others. However others are also contemplated. The encoded sympathomimetic receptors and parasympathomimetic receptors include acetylcholinesterase receptors (AcChaseR) acetylcholine receptors (AcChR), atropine receptors, muscarinic receptors, epinephrine receptors (EpiR), dopamine receptors (DOPAR), and norepinephrine receptors (NEpiR), among others. Further examples of encoded receptors are adenosine A<sub>1</sub> receptor, adenosine A<sub>2b</sub> receptor, adenosine A<sub>3</sub> receptor, endothelin receptor A, endothelin receptor B, IgE high affinity receptor, muscarinic acetylcholine receptors, substance P receptor, histamine receptor, CCR-1 CC chemokine receptor, CCR-2 CC chemokine receptor, CCR-3 CC chemokine receptor (Eotaxin Receptor), interleukin-1 $\beta$  receptor (IL-1 $\beta$ R), interleukin-1 receptor (IL-1R), interleukin-1 $\beta$  receptor (IL-1 $\beta$ R), interleukin-3 receptor (IL-3R), CCR-4 CC chemokine receptor, cysteinyl leukotriene receptors, prostanoid receptors, GATA-3 transcription factor receptor, interleukin-1 receptor (IL-1R), interleukin-4 receptor (IL-4R), interleukin-5 receptor (IL-5R), interleukin-8 receptor (IL-8R), interleukin-9 receptor (IL-9R), interleukin-11 receptor (IL-11R), sympathomimetic receptors, parasympathomimetic receptors, GABA receptors, adenosine receptors, bradykinin receptors, e.g. bradykinin B2 receptor, insulin receptors, glucagon receptors, prostaglandin receptors, thyroid receptors, androgen receptors, anabolic receptors, estrogen receptors, progesterone receptors, receptors associated with the coagulation cascade, adenohipophyseal receptors, and histamine receptors (HisR). Others are also contemplated even though not listed herein. The encoded enzymes for development of the oligos of the invention include synthetases, kinases, oxidases, phosphatases, reductases, polysaccharide, triglyceride, and protein hydrolases, esterases, elastases, and , polysaccharide, triglyceride, lipid, and protein synthases, among others. Examples of target enzymes are tryptase, inducible nitric oxide synthase, cyclooxygenase (Cox), MAP kinase, eosinophil peroxidase,  $\beta$ 2-adrenergic receptor kinase, leukotriene c-4 synthase, 5-lipoxygenase, phosphodiesterase IV, metalloproteinase, tryptase, CSBP/p38 MAP kinase, neutrophil elastase, phospholipase A<sub>2</sub>, cyclooxygenase 2 (Cox-2), fucosyl transferase, chymase, protein kinase C, thymidylate synthetase, dihydrofolate reductase, thymidine kinase, deoxycytidine kinase, and ribonucleotide reductase, among others. Any enzyme associated with a disease or condition, however, is suitable as a target for this invention. Suitable encoded factors for application of this invention are, among others, Nf $\kappa$ B transcription factor, granulocyte macrophage colony stimulating factor (GM-CSF), AP-1 transcription factor, GATA-3 transcription factor, monocyte activating factor, neutrophil chemotactic factor, granulocyte/macrophage colony-stimulating-factor (G-CSF), NFAT transcription factors, platelet activating factor, tumor necrosis factor  $\alpha$  (TNF  $\alpha$ ), and basic fibroblast growth factor (BFGF). Additional factors are also within the invention even though not specifically mentioned. Suitable adhesion molecules for use with this invention include intracellular adhesion molecules 1 (ICAM-1), 2 (ICAM-2) and 3 (ICAM-3), vascular cellular adhesion molecule (VCAM), endothelial leukocyte adhesion molecule-1 (ELAM-1), neutrophil adherence receptor, mad CAM-1, and the like. Other known and unknown factors (at this time) may also be targeted herein. Among the cytokines, lymphokines and chemokines preferred are interleukin-1 (IL-1), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-8 (IL-8),

interleukin-9 (IL-9), interleukin-11 (IL-11), CCR-5 CC chemokine, and Rantes. Other examples include H2A histone family, member N, Tubulin, beta polypeptide, ELL gene (11-19 lysine-rich leukemia gene) 7-dehydrocholesterol reductase, ADP-ribosylation factor-like 7, Karyopherin alpha 2 (RAG cohort 1, importin alpha 1), EST (AI038433), EST (AI122689), EST (AI092623), ESTs (AI095492), ESTs (AI138216), ESTs (AI128305), ESTs (AI125228), ESTs (AI041482), ESTs (AI051839), Homo sapiens mRNA; cDNA DKFZp434A1716, ESTs (AI096522), ESTs (AI122807), ESTs (AI041212), EST (AI125651), Enolase 1, (alpha), EST (AI024215), EST (AI034360), Homo sapiens mRNA; cDNA DKFZp564H0764, Homo sapiens mRNA for KIAA1363 protein, partial cds, Potassium voltage-gated channel, shaker-related subfamily, beta member 2, ER-associated DNAJ; ER-associated Hsp40 co-chaperone; hDj9; ERj3, ESTs, Weakly similar to p38 protein [H.sapiens] (AA906703), CGI-142, ESTs (AA463249), Homo sapiens clone 25058 mRNA sequence ESTs (R49144), Squamous cell carcinoma antigen 1, ESTs (AA425700), Myosin X, ESTs (AA459692), Epithelial protein lost in neoplasm beta, CD44 antigen (homing function and Indian blood group system), Coagulation factor III (thromboplastin, tissue factor), ESTs (AA909635), Adducin 1 (alpha), 5' Nucleotidase (CD73), ESTs, Moderately similar to semaphorin C [M.musculus] (AA293300), ESTs (AA278764), ESTs (AA678160), Calmodulin 2 (phosphorylase kinase, delta), ESTs (R42770), Chloride intracellular channel 1, High-mobility group (nonhistone chromosomal) protein 17, Ubiquitin carrier protein, Tubulin, alpha 1 (testis specific), Transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase), Sparc/osteonectin, cwcw and kazal-like domains proteoglycan (testican), Proteasome (prosome, macropain) 26S subunit, non-ATPase, 2, Tubulin, beta polypeptide, Filamin B, beta (actin-binding protein-278), Stanniocalcin, Low density lipoprotein receptor (familial hypercholesterolemia), Plectin 1, intermediate filament binding protein, 500kD, S100 calcium-binding protein A2, Immediate early response 3, Calpain, large polypeptide L2, Pleckstrin homology-like domain, family A, member 1, Melanoma adhesion molecule, CD44 antigen (homing function and Indian blood group system), Programmed cell death 5, Hexokinase 1, Vascular endothelial growth factor, Integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor), Cahumenin, Syntaxin 11, Diphtheria toxin receptor (heparin-binding epidermal growth factor-like growth factor), Fn14 for type I transmembrane protein, Nef-associated factor 1, High-mobility group (nonhistone chromosomal) protein isoforms I and Y, Catechol-O-methyltransferase, C-terminal binding protein 1, Collagen, type XVII, alpha 1, ESTs (N58473), Farnesyl-diphosphate farnesyltransferase 1 RNA helicase-related protein, Interferon stimulated gene (20kD), Steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1), Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase), Laminin, alpha 3 (nicein (150kD), kalinin (165kD), BM600 (150kD), epilegrin), Collagen, type XVII, alpha 1, Keratin 18, Heparan sulfate (glucosamine) 3-O-sulfotransferase 1, Tubulin, alpha 2, Adenylyl cyclase-associated protein, Forkhead box D1, Cathepsin C, ESTs, Highly similar to AF151802\_1 CGI-44 protein [H.sapiens] (T74688), Ribonucleotide reductase M2 polypeptide, Laminin, gamma 2 (nicein (100kD), kalinin (105kD), BM600 (100kD), Herlitz junctional epidermolysis bullosa)), Homo sapiens mRNA; cDNA DKFZp586P1622 (from clone DKFZp586P1622), ESTs, Weakly similar to /prediction (AA284245), and Lactate dehydrogenase A. Others, however, may also be targeted, as they are known to be involved in specific diseases or conditions to be treated, or for their generic activities, such as inflammation. Examples of defensins for the practice of this invention are defensin 1, defensin 2, and defensin 3, and of selectins are  $\alpha 4\beta 1$  selectin,  $\alpha 4\beta 7$  selectin, LFA-1 selectin, E-selectin, P-selectin, and L-selectin. Examples of oncogenes, although not an all inclusive list, are ras, src, myc, and bcBCL. Others, however, are also suitable for use with this invention.

The agents administered in accordance with this invention are preferably designed to be anti-sense to one or more target genes and/or mRNAs usually related in origin to the species to which it is to be administered, although they may be directed, to foreign sequences, e.g. of viruses. When treating humans, the agents are preferably designed to be anti-sense to a human gene or RNA. The agents of the invention encompass oligonucleotides which are anti-sense to naturally occurring DNA and/or RNA sequences, fragments thereof of up to a length of one (1) base less than the targeted sequence, preferably at least about 7 nucleotides long, oligos having only over about 0.02%, more preferably over about 0.1%, still more preferably over about 1%, and even more preferably over about 4% adenosine nucleotides, and up to about 30%, more preferably up to about 15%, still more preferably up to about 10% and even more preferably up to about 5%, adenosine nucleotide, or lacking adenosine altogether, and oligos in which one or more of the adenosine nucleotides have been replaced with so-called universal bases, which may pair up with thymidine or uridine nucleotides but fail to substantially trigger adenosine receptor activity. Examples of human sequences and fragments, which are not limiting, of anti-sense oligonucleotide of the

invention are the following fragments as well as shorter segments of the fragments and of the full gene or mRNA coding sequences, exons and intron-exon junctions encompassing preferably 7, 10, 15, 18 to 21, 24, 27, 30, n-1 nucleotides for each sequence, where n is the sequence's total number of nucleotides. These fragments may be selected from any portion of the longer oligo, for example, from the middle, 5'- end, 3'- end or starting at any other site of the original sequence. Of particular importance are fragments of low adenosine nucleotide content, that is, those fragments containing less than or about 30%, preferably less than or about 15%, more preferably less than or about 10%, and even more preferably less than or about 5%, and most preferably those devoid of adenosine nucleotide, either by choice or by replacement with a universal base in accordance with this invention. The agent of the invention includes as a most preferred group sequences and their fragments where one or more adenines present in the sequence have been replaced by a universal base (B), as exemplified here. Similarly, also encompassed are all shorter fragments of the B-containing fragments designed by substitution of B(s) for adenosine(s) (A(s)) contained in the sequences, fragments thereof or segments thereof, as described above. A limited list of sequences and fragments is provided below.

Some of the examples of anti-sense oligonucleotide sequence fragments target the initiation codon of the respective gene, and in some cases adenosine is substituted with a universal or alternative base adenosine analogue denoted as "B", which lacks ability to bind to the adenosine A<sub>1</sub> and/or A<sub>3</sub> receptors. In fact, such replacement nucleotide acts as a "spacer". Many of the examples shown below provide one such sequence and many fragments overlapping the initiation codon, preferably wherein the number of nucleotides n is about 7, about 10, about 12, about 15, about 18, about 21 and up to about 28, about 35, about 40, about 50, about 60.

#### **Human Receptor-related Antisense Polynucleotide**

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5 Human Enzyme-related Antisense Polynucleotide  
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**Human Factor Related Anti-sense Oligonucleotide**

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	TCTCTCCAA	AAATAAGCCC	TCAGGAGGGG	ACAAAGTTGA	CCGCTGATTG	AGCCTGTCAG	GGCTGTGCAC-3'	(SEQ ID NO:12373)
<b>Human Adenosine A1 Receptor Nucleic Acid and Antisense Oligonucleotide Fragments</b>								
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 45 TTTGCTGGAG TGCTGGCTCC AGCCCTGGG GAGTGAAGTT GGTGCGGTAG GTGCTGGCCT CAAACAGCCA CGAGGTGGTA  
 GCTCTGAGCC CTCTTCTTTG CCCTGAGCTT TCCGGGGAGG AGCCTGGAGT GTAATTACCT GTCATCTGGG CCACAGCTC  
 CACTGGCCCC CGTTGCCGGG CTTGGACTGT CCGTGTGAC CCCATCTCTG CTGCTTCTGG GCCTGATGGA TCCCATGAGC  
 CTAGACATGC CAACTCGGGA GCATTCTGCC TGCTGGGAA CCGGGTGGAC GAGGGAGTGT CTGTAAGGAC TCAGTGTGTA  
 CTGTAGGCGC CCCTGGGGTG GTTTTAGCAG GCTGCAGCAG GCAGAGGAGG AGTACCCCCC TGAGAGCATG TGGGGGAAGG  
 50 CCGGGGTCT AGGACTTTAG GGATCTGGGA TCTGGGGAAG GACCAACCCA TGCCCTGCCA AGCCTGGAGC CCCTGTGTTG  
 GGGGGCAAGG TGGGGGAGCC TGGAGCCCT GTGTGGGAGG GCGAGGCGGG GGAGCCTGGA GCCCTGTGT GGGAGGGCGA  
 GGGGGGGAT CTTGGAGCCC CTGTGTCCGG GGGCGAGGGA GGGGAGGTGG CCGTCCGTTG ACCTTCTGAA CATGAGTGTG  
 AACTCCAGGA CTGTCTTCCA AGCCCTTCCC TCTGTTGGAA ATTGGTGTG CCCTGGCTCC CAAGGGAGGC CCATGTGACT  
 55 AATAAAAAAC TGTGAACCCT -3' (FRAG. NO: ) (SEQ ID NO:11790)  
 5'-ATGCCCGCCT CCATCTCAGC TTTCCAGGCC GCCTACATCG GCATCGAGGT GCTCATCGCC CTGGTCTCTG TGCCCGGGAA  
 CGTGTCTGGT ATCTGGGCGG TGAAGGTGAA CCAGGCGCTG CCGGATGCCA CCTTCTGCTT CATCGTCTCG CTGGCGGTGG  
 CTGATGTGGC CGTGGGTGCC CTGGTATCC CCTCGCCAT CCTCATCAAC ATTGGGCCAC AGACCTACTT CCACACTGTC  
 60 CTCATGGTTG CCGTGTCCGT CCTCATCTC ACCCAGAGCT CCATCCTGGC CTGCTGGCA ATTGCTGTGG ACCGCTACCT  
 CCGGGTCAAG ATCCCTCTCC GGTACAAGAT GGTGGTGAAC CCGCGGAGGG CGGCGGTGGC CATAGCCGGC TGCTGGATCC  
 TCTCCTCTGT GGTGGGACTG CCCCTATGT TTGGCTGGAA CAATCTGAGT GCGGTGGAGC GGGCTGGGC AGCCAACGGC  
 AGCATGGGGG AGCCCGTGAT CAAGTGGGAG TTCGAGAAGG TCATCAGCAT GGAGTACATG GTCTACTTCA ACTTCTTGT  
 GTGGGTGCTG CCCCCGCTTC TCCTCATGGT CCTCATCTAC CTGGAGGTCT TCTACCTAAT CCGCAAGCAG CTCAACAAGA  
 AGGTGTGGGC CTCTCCGGC GACCCGAGA AGTACTATGG GAAGGAGCTG AAGATCGCCA AGTGCCTGGC CCTCATCTC  
 65 TTTCTCTTGG CCTCAGCTG CTGCTTTTG AGTACTTCA ACTGCATCAC CCTTCTTCTG CCGTCTGCTG ACAAGCCAG  
 CATCCTTACC TACATTGCCA TCTTCTCAC GCACGGCAAC TCGGCCATGA ACCCATTTGT CTATGCTTTC CGCATCCAGA  
 AGTTCGCGT CACCTTCTT AAGATTGGA ATGACCATTT CCGCTGCCAG CCGTGCACCTC CCATTGACGA GGATCTCCCA  
 GAAGAGAGGC CTGATGACTA G (FRAG. NO: ) (SEQ ID NO:12483)  
 5'-GAT GGA GGG CGG CAT GGC GGG-3' (FRAG. NO: 1657) (SEQ ID NO:11781)  
 70 5'-G CGG GTC GCC GG-3' (FRAG. NO: 1658) (SEQ ID NO:11782)  
 5'-GGC GGG CBC BGG C-3' (FRAG. NO: 1659) (SEQ ID NO:11783)  
 5'-GGC GGG CBC-3' (FRAG. NO: 1660) (SEQ ID NO:11784)  
 5'-GC GGC CTG G-3' (FRAG. NO: 1661) (SEQ ID NO:11785)  
 5'-GGB GGG CGG C-3' (FRAG. NO: 1662) (SEQ ID NO:11786)  
 75 5'-GBT GGB GGG-3' (FRAG. NO: 1663) (SEQ ID NO:11787)



[illegible]

- 5'-GGC GGC CTG GAA AGC TGA G-3' (FRAG 75) (SEQ ID NO:9454)  
5'-GGC GGC CTG GAA AGC TGA-3' (FRAG 76) (SEQ ID NO:9455)  
5'-GGC GGC CTG GAA AGC TG-3' (FRAG 77) (SEQ ID NO:9456)  
5'-GGC GGC CTG GAA AGC T-3' (FRAG 78) (SEQ ID NO:9457)  
5 5'-GGC GGC CTG GAA AGC-3' (FRAG 79) (SEQ ID NO:9458)  
5'-GGC GGC CTG GAA AG-3' (FRAG 80) (SEQ ID NO:9459)  
5'-GGC GGC CTG GAA A-3' (FRAG 81) (SEQ ID NO:9460)  
5'-GGC GGC CTG GAA-3' (FRAG 82) (SEQ ID NO:9461)  
5'-GGC GGC CTG GA-3' (FRAG 83) (SEQ ID NO:9462)  
10 5'-GGC GGC CTG G-3' (FRAG 84) (SEQ ID NO:9463)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 85) (SEQ ID NO:9464)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 86) (SEQ ID NO:9465)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 87) (SEQ ID NO:9466)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 88) (SEQ ID NO:9467)  
15 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 89) (SEQ ID NO:9468)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 90) (SEQ ID NO:9469)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 91) (SEQ ID NO:9470)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 92) (SEQ ID NO:9471)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 93) (SEQ ID NO:9472)  
20 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 94) (SEQ ID NO:9473)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 95) (SEQ ID NO:9474)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 96) (SEQ ID NO:9475)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 97) (SEQ ID NO:9476)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 98) (SEQ ID NO:9477)  
25 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 99) (SEQ ID NO:9478)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 100) (SEQ ID NO:9479)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 101) (SEQ ID NO:9480)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 102) (SEQ ID NO:9481)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 103) (SEQ ID NO:9482)  
30 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 104) (SEQ ID NO:9483)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 105) (SEQ ID NO:9484)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 106) (SEQ ID NO:9485)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 107) (SEQ ID NO:9486)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 108) (SEQ ID NO:9487)  
35 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 109) (SEQ ID NO:9488)  
5'-GC GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 110) (SEQ ID NO:9489)  
5'-GC GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 111) (SEQ ID NO:9490)  
5'-GC GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 112) (SEQ ID NO:9491)  
5'-GC GGC CTG GAA AGC TGA GAT GG -3' (FRAG 113) (SEQ ID NO:9492)  
40 5'-GC GGC CTG GAA AGC TGA GAT G -3' (FRAG 114) (SEQ ID NO:9493)  
5'-GC GGC CTG GAA AGC TGA GAT -3' (FRAG 115) (SEQ ID NO:9494)  
5'-GC GGC CTG GAA AGC TGA GA-3' (FRAG 116) (SEQ ID NO:9495)  
5'-GC GGC CTG GAA AGC TGA G-3' (FRAG 117) (SEQ ID NO:9496)  
5'-GC GGC CTG GAA AGC TGA-3' (FRAG 118) (SEQ ID NO:9497)  
45 5'-GC GGC CTG GAA AGC TG-3' (FRAG 119) (SEQ ID NO:9498)  
5'-GC GGC CTG GAA AGC T-3' (FRAG 120) (SEQ ID NO:9499)  
5'-GC GGC CTG GAA AGC-3' (FRAG 121) (SEQ ID NO:9500)  
5'-GC GGC CTG GAA AG-3' (FRAG 122) (SEQ ID NO:9501)  
5'-GC GGC CTG GAA A-3' (FRAG 123) (SEQ ID NO:9502)  
50 5'-GC GGC CTG GAA-3' (FRAG 124) (SEQ ID NO:9503)  
5'-GC GGC CTG GA-3' (FRAG 125) (SEQ ID NO:9504)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 126) (SEQ ID NO:9505)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 127) (SEQ ID NO:9506)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 128) (SEQ ID NO:9507)  
55 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 129) (SEQ ID NO:9508)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 130) (SEQ ID NO:9509)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 131) (SEQ ID NO:9510)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 132) (SEQ ID NO:9511)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 133) (SEQ ID NO:9512)  
60 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 134) (SEQ ID NO:9513)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 135) (SEQ ID NO:9514)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 136) (SEQ ID NO:9515)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 137) (SEQ ID NO:9516)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 138) (SEQ ID NO:9517)  
65 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 139) (SEQ ID NO:9518)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 140) (SEQ ID NO:9519)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 141) (SEQ ID NO:9520)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 142) (SEQ ID NO:9521)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 143) (SEQ ID NO:9522)  
70 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 144) (SEQ ID NO:9523)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 145) (SEQ ID NO:9524)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 146) (SEQ ID NO:9525)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 147) (SEQ ID NO:9526)  
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 148) (SEQ ID NO:9527)  
75 5'-C GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 148) (SEQ ID NO:9528)

- 5'-C GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 150) (SEQ ID NO:9529)  
5'-C GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 151) (SEQ ID NO:9530)  
5'-C GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 152) (SEQ ID NO:9531)  
5'-C GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 153) (SEQ ID NO:9532)  
5 5'-C GGC CTG GAA AGC TGA GAT GG -3' (FRAG 154) (SEQ ID NO:9533)  
5'-C GGC CTG GAA AGC TGA GAT G -3' (FRAG 155) (SEQ ID NO:9534)  
5'-C GGC CTG GAA AGC TGA GAT -3' (FRAG 156) (SEQ ID NO:9535)  
5'-C GGC CTG GAA AGC TGA GA-3' (FRAG 157) (SEQ ID NO:9536)  
5'-C GGC CTG GAA AGC TGA G-3' (FRAG 158) (SEQ ID NO:9537)  
10 5'-C GGC CTG GAA AGC TGA-3' (FRAG 159) (SEQ ID NO:9538)  
5'-C GGC CTG GAA AGC TG-3' (FRAG 160) (SEQ ID NO:9539)  
5'-C GGC CTG GAA AGC T-3' (FRAG 161) (SEQ ID NO:9540)  
5'-C GGC CTG GAA AGC-3' (FRAG 162) (SEQ ID NO:9541)  
5'-C GGC CTG GAA AG-3' (FRAG 163) (SEQ ID NO:9542)  
15 5'-C GGC CTG GAA A-3' (FRAG 164) (SEQ ID NO:9543)  
5'-C GGC CTG GAA-3' (FRAG 165) (SEQ ID NO:9544)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 166) (SEQ ID NO:9545)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 167) (SEQ ID NO:9546)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 168) (SEQ ID NO:9547)  
20 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 169) (SEQ ID NO:9548)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 170) (SEQ ID NO:9549)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 171) (SEQ ID NO:9550)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 172) (SEQ ID NO:9551)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 173) (SEQ ID NO:9552)  
25 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 174) (SEQ ID NO:9553)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG CAC-3' (FRAG 175) (SEQ ID NO:9554)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 176) (SEQ ID NO:9555)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG C-3' (FRAG 177) (SEQ ID NO:9556)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG -3' (FRAG 178) (SEQ ID NO:9557)  
30 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GG-3' (FRAG 179) (SEQ ID NO:9558)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC G-3' (FRAG 180) (SEQ ID NO:9559)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC -3' (FRAG 181) (SEQ ID NO:9560)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 182) (SEQ ID NO:9561)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 183) (SEQ ID NO:9562)  
35 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 184) (SEQ ID NO:9563)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 185) (SEQ ID NO:9564)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 186) (SEQ ID NO:9565)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 187) (SEQ ID NO:9566)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 188) (SEQ ID NO:9567)  
40 5'- GGC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 189) (SEQ ID NO:9568)  
5'- GGC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 190) (SEQ ID NO:9569)  
5'- GGC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 191) (SEQ ID NO:9570)  
5'- GGC CTG GAA AGC TGA GAT GGA G -3' (FRAG 192) (SEQ ID NO:9571)  
5'- GGC CTG GAA AGC TGA GAT GGA -3' (FRAG 193) (SEQ ID NO:9572)  
45 5'- GGC CTG GAA AGC TGA GAT GG -3' (FRAG 194) (SEQ ID NO:9573)  
5'- GGC CTG GAA AGC TGA GAT G -3' (FRAG 195) (SEQ ID NO:9574)  
5'- GGC CTG GAA AGC TGA GAT -3' (FRAG 196) (SEQ ID NO:9575)  
5'- GGC CTG GAA AGC TGA GA-3' (FRAG 197) (SEQ ID NO:9576)  
5'- GGC CTG GAA AGC TGA G-3' (FRAG 198) (SEQ ID NO:9577)  
50 5'- GGC CTG GAA AGC TGA-3' (FRAG 199) (SEQ ID NO:9578)  
5'- GGC CTG GAA AGC TG-3' (FRAG 200) (SEQ ID NO:9579)  
5'- GGC CTG GAA AGC T-3' (FRAG 201) (SEQ ID NO:9580)  
5'- GGC CTG GAA AGC-3' (FRAG 202) (SEQ ID NO:9581)  
5'- GGC CTG GAA AG-3' (FRAG 203) (SEQ ID NO:9582)  
55 5'- GGC CTG GAA A-3' (FRAG 204) (SEQ ID NO:9583)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 205) (SEQ ID NO:9584)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 206) (SEQ ID NO:9585)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 207) (SEQ ID NO:9586)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 208) (SEQ ID NO:9587)  
60 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 209) (SEQ ID NO:9588)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 210) (SEQ ID NO:9589)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 211) (SEQ ID NO:9590)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG CAC AG-3' (FRAG 212) (SEQ ID NO:9591)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG CAC A-3' (FRAG 213) (SEQ ID NO:9592)  
65 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG CAC-3' (FRAG 214) (SEQ ID NO:9593)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG CA-3' (FRAG 215) (SEQ ID NO:9594)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG C-3' (FRAG 216) (SEQ ID NO:9595)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GGG -3' (FRAG 217) (SEQ ID NO:9596)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC GG-3' (FRAG 218) (SEQ ID NO:9597)  
70 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC G-3' (FRAG 219) (SEQ ID NO:9598)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT TGC -3' (FRAG 220) (SEQ ID NO:9599)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 221) (SEQ ID NO:9600)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 222) (SEQ ID NO:9601)  
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 223) (SEQ ID NO:9602)  
75 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 224) (SEQ ID NO:9603)

- 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 225) (SEQ ID NO:9604)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 226) (SEQ ID NO:9605)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 227) (SEQ ID NO:9606)  
 5'- GC CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 228) (SEQ ID NO:9607)  
 5 5'- GC CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 229) (SEQ ID NO:9608)  
 5'- GC CTG GAA AGC TGA GAT GGA GG -3' (FRAG 230) (SEQ ID NO:9609)  
 5'- GC CTG GAA AGC TGA GAT GGA G -3' (FRAG 231) (SEQ ID NO:9610)  
 5'- GC CTG GAA AGC TGA GAT GGA -3' (FRAG 232) (SEQ ID NO:9611)  
 5'- GC CTG GAA AGC TGA GAT GG -3' (FRAG 233) (SEQ ID NO:9612)  
 10 5'- GC CTG GAA AGC TGA GAT G -3' (FRAG 234) (SEQ ID NO:9613)  
 5'- GC CTG GAA AGC TGA GAT -3' (FRAG 235) (SEQ ID NO:9614)  
 5'- GC CTG GAA AGC TGA GA-3' (FRAG 236) (SEQ ID NO:9615)  
 5'- GC CTG GAA AGC TGA G-3' (FRAG 237) (SEQ ID NO:9616)  
 5'- GC CTG GAA AGC TGA-3' (FRAG 238) (SEQ ID NO:9617)  
 15 5'- GC CTG GAA AGC TG-3' (FRAG 239) (SEQ ID NO:9618)  
 5'- GC CTG GAA AGC T-3' (FRAG 240) (SEQ ID NO:9619)  
 5'- GC CTG GAA AGC-3' (FRAG 241) (SEQ ID NO:9620)  
 5'- GC CTG GAA AG-3' (FRAG 242) (SEQ ID NO:9621)  
 5'- C CTG GAA AGC TGA GAT GG A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 243) (SEQ ID NO:9622)  
 20 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 244) (SEQ ID NO:9623)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 245) (SEQ ID NO:9624)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 246) (SEQ ID NO:9625)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 247) (SEQ ID NO:9626)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 248) (SEQ ID NO:9627)  
 25 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 249) (SEQ ID NO:9628)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 250) (SEQ ID NO:9629)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 251) (SEQ ID NO:9630)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 252) (SEQ ID NO:9631)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 253) (SEQ ID NO:9632)  
 30 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 254) (SEQ ID NO:9633)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 255) (SEQ ID NO:9634)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 256) (SEQ ID NO:9635)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 257) (SEQ ID NO:9636)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 258) (SEQ ID NO:9637)  
 35 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 259) (SEQ ID NO:9638)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 260) (SEQ ID NO:9639)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 261) (SEQ ID NO:9640)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 262) (SEQ ID NO:9641)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 263) (SEQ ID NO:9642)  
 40 5'- C CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 264) (SEQ ID NO:9643)  
 5'- C CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 265) (SEQ ID NO:9644)  
 5'- C CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 266) (SEQ ID NO:9645)  
 5'- C CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 267) (SEQ ID NO:9646)  
 5'- C CTG GAA AGC TGA GAT GGA GG -3' (FRAG 268) (SEQ ID NO:9647)  
 45 5'- C CTG GAA AGC TGA GAT GGA G -3' (FRAG 269) (SEQ ID NO:9648)  
 5'- C CTG GAA AGC TGA GAT GGA -3' (FRAG 270) (SEQ ID NO:9649)  
 5'- C CTG GAA AGC TGA GAT GG -3' (FRAG 271) (SEQ ID NO:9650)  
 5'- C CTG GAA AGC TGA GAT G -3' (FRAG 272) (SEQ ID NO:9651)  
 5'- C CTG GAA AGC TGA GAT -3' (FRAG 273) (SEQ ID NO:9652)  
 50 5'- C CTG GAA AGC TGA GA-3' (FRAG 274) (SEQ ID NO:9653)  
 5'- C CTG GAA AGC TGA G-3' (FRAG 275) (SEQ ID NO:9654)  
 5'- C CTG GAA AGC TGA-3' (FRAG 276) (SEQ ID NO:9655)  
 5'- C CTG GAA AGC TG-3' (FRAG 277) (SEQ ID NO:9656)  
 5'- C CTG GAA AGC T-3' (FRAG 278) (SEQ ID NO:9657)  
 55 5'- C CTG GAA AGC-3' (FRAG 279) (SEQ ID NO:9658)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 280) (SEQ ID NO:9659)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 281) (SEQ ID NO:9660)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 282) (SEQ ID NO:9661)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 283) (SEQ ID NO:9662)  
 60 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 284) (SEQ ID NO:9663)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 285) (SEQ ID NO:9664)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 286) (SEQ ID NO:9665)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 287) (SEQ ID NO:9666)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 288) (SEQ ID NO:9667)  
 65 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 289) (SEQ ID NO:9668)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 290) (SEQ ID NO:9669)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 291) (SEQ ID NO:9670)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 292) (SEQ ID NO:9671)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 293) (SEQ ID NO:9672)  
 70 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 294) (SEQ ID NO:9673)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 295) (SEQ ID NO:9674)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 296) (SEQ ID NO:9675)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 297) (SEQ ID NO:9676)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 298) (SEQ ID NO:9677)  
 75 5'- CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 299) (SEQ ID NO:9678)

- 5'- CTG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 300) (SEQ ID NO:9679)  
 5'- CTG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 301) (SEQ ID NO:9680)  
 5'- CTG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 302) (SEQ ID NO:9681)  
 5'- CTG GAA AGC TGA GAT GGA GGG C -3' (FRAG 303) (SEQ ID NO:9682)  
 5 5'- CTG GAA AGC TGA GAT GGA GGG -3' (FRAG 304) (SEQ ID NO:9683)  
 5'- CTG GAA AGC TGA GAT GGA GG -3' (FRAG 305) (SEQ ID NO:9684)  
 5'- CTG GAA AGC TGA GAT GGA G -3' (FRAG 306) (SEQ ID NO:9685)  
 5'- CTG GAA AGC TGA GAT GGA -3' (FRAG 307) (SEQ ID NO:9686)  
 5'- CTG GAA AGC TGA GAT GG -3' (FRAG 308) (SEQ ID NO:9687)  
 10 5'- CTG GAA AGC TGA GAT G -3' (FRAG 309) (SEQ ID NO:9688)  
 5'- CTG GAA AGC TGA GAT -3' (FRAG 310) (SEQ ID NO:9689)  
 5'- CTG GAA AGC TGA GA-3' (FRAG 311) (SEQ ID NO:9690)  
 5'- CTG GAA AGC TGA G-3' (FRAG 312) (SEQ ID NO:9691)  
 5'- CTG GAA AGC TGA-3' (FRAG 313) (SEQ ID NO:9692)  
 15 5'- CTG GAA AGC TG-3' (FRAG 314) (SEQ ID NO:9693)  
 5'- CTG GAA AGC T-3' (FRAG 315) (SEQ ID NO:9694)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 316) (SEQ ID NO:9695)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 317) (SEQ ID NO:9696)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 318) (SEQ ID NO:9697)  
 20 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 319) (SEQ ID NO:9698)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 320) (SEQ ID NO:9699)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 321) (SEQ ID NO:9700)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 322) (SEQ ID NO:9701)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 323) (SEQ ID NO:9702)  
 25 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 324) (SEQ ID NO:9703)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 325) (SEQ ID NO:9704)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 326) (SEQ ID NO:9705)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 327) (SEQ ID NO:9706)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 328) (SEQ ID NO:9707)  
 30 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 329) (SEQ ID NO:9708)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 330) (SEQ ID NO:9709)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 331) (SEQ ID NO:9710)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 332) (SEQ ID NO:9711)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 333) (SEQ ID NO:9712)  
 35 5'- TG GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 334) (SEQ ID NO:9713)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 335) (SEQ ID NO:9714)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 336) (SEQ ID NO:9715)  
 5'- TG GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 337) (SEQ ID NO:9716)  
 5'- TG GAA AGC TGA GAT GGA GGG CG -3' (FRAG 338) (SEQ ID NO:9717)  
 40 5'- TG GAA AGC TGA GAT GGA GGG C -3' (FRAG 339) (SEQ ID NO:9718)  
 5'- TG GAA AGC TGA GAT GGA GGG -3' (FRAG 340) (SEQ ID NO:9719)  
 5'- TG GAA AGC TGA GAT GGA GG -3' (FRAG 341) (SEQ ID NO:9720)  
 5'- TG GAA AGC TGA GAT GGA G -3' (FRAG 342) (SEQ ID NO:9721)  
 5'- TG GAA AGC TGA GAT GGA -3' (FRAG 343) (SEQ ID NO:9722)  
 45 5'- TG GAA AGC TGA GAT GG -3' (FRAG 344) (SEQ ID NO:9723)  
 5'- TG GAA AGC TGA GAT G -3' (FRAG 345) (SEQ ID NO:9724)  
 5'- TG GAA AGC TGA GAT -3' (FRAG 346) (SEQ ID NO:9725)  
 5'- TG GAA AGC TGA GA-3' (FRAG 347) (SEQ ID NO:9726)  
 5'- TG GAA AGC TGA G-3' (FRAG 348) (SEQ ID NO:9727)  
 50 5'- TG GAA AGC TGA-3' (FRAG 349) (SEQ ID NO:9728)  
 5'- TG GAA AGC TG-3' (FRAG 350) (SEQ ID NO:9729)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 351) (SEQ ID NO:9730)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 352) (SEQ ID NO:9731)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 353) (SEQ ID NO:9732)  
 55 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 354) (SEQ ID NO:9733)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 355) (SEQ ID NO:9734)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 356) (SEQ ID NO:9735)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 357) (SEQ ID NO:9736)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 358) (SEQ ID NO:9737)  
 60 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 359) (SEQ ID NO:9738)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 360) (SEQ ID NO:9739)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 361) (SEQ ID NO:9740)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 362) (SEQ ID NO:9741)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 363) (SEQ ID NO:9742)  
 65 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 364) (SEQ ID NO:9743)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 365) (SEQ ID NO:9744)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 366) (SEQ ID NO:9745)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 367) (SEQ ID NO:9746)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 368) (SEQ ID NO:9747)  
 70 5'- G GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 369) (SEQ ID NO:9748)  
 5'- G GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 370) (SEQ ID NO:9749)  
 5'- G GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 371) (SEQ ID NO:9750)  
 5'- G GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 372) (SEQ ID NO:9751)  
 5'- G GAA AGC TGA GAT GGA GGG CG -3' (FRAG 373) (SEQ ID NO:9752)  
 75 5'- G GAA AGC TGA GAT GGA GGG C -3' (FRAG 374) (SEQ ID NO:9753)

- 5'- G GAA AGC TGA GAT GGA GGG -3' (FRAG 375) (SEQ ID NO:9754)  
5'- G GAA AGC TGA GAT GGA GG -3' (FRAG 376) (SEQ ID NO:9755)  
5'- G GAA AGC TGA GAT GGA G -3' (FRAG 377) (SEQ ID NO:9756)  
5'- G GAA AGC TGA GAT GGA -3' (FRAG 378) (SEQ ID NO:9757)  
5'- G GAA AGC TGA GAT GG -3' (FRAG 379) (SEQ ID NO:9758)  
5'- G GAA AGC TGA GAT G -3' (FRAG 380) (SEQ ID NO:9759)  
5'- G GAA AGC TGA GAT -3' (FRAG 381) (SEQ ID NO:9760)  
5'- G GAA AGC TGA GA-3' (FRAG 382) (SEQ ID NO:9761)  
5'- G GAA AGC TGA G-3' (FRAG 383) (SEQ ID NO:9762)  
5'- G GAA AGC TGA-3' (FRAG 384) (SEQ ID NO:9763)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 385) (SEQ ID NO:9764)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 386) (SEQ ID NO:9765)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 387) (SEQ ID NO:9766)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 388) (SEQ ID NO:9767)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 389) (SEQ ID NO:9768)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 390) (SEQ ID NO:9769)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 391) (SEQ ID NO:9770)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 392) (SEQ ID NO:9771)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 393) (SEQ ID NO:9772)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 394) (SEQ ID NO:9773)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 395) (SEQ ID NO:9774)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 396) (SEQ ID NO:9775)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 397) (SEQ ID NO:9776)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 398) (SEQ ID NO:9777)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 399) (SEQ ID NO:9778)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 400) (SEQ ID NO:9779)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 401) (SEQ ID NO:9780)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 402) (SEQ ID NO:9781)  
5'- GAA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 403) (SEQ ID NO:9782)  
5'- GAA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 404) (SEQ ID NO:9783)  
5'- GAA AGC TGA GAT GGA GGG CGG C-3' (FRAG 405) (SEQ ID NO:9784)  
5'- GAA AGC TGA GAT GGA GGG CGG -3' (FRAG 406) (SEQ ID NO:9785)  
5'- GAA AGC TGA GAT GGA GGG CG -3' (FRAG 407) (SEQ ID NO:9786)  
5'- GAA AGC TGA GAT GGA GGG C -3' (FRAG 408) (SEQ ID NO:9787)  
5'- GAA AGC TGA GAT GGA GGG -3' (FRAG 409) (SEQ ID NO:9788)  
5'- GAA AGC TGA GAT GGA GG -3' (FRAG 410) (SEQ ID NO:9789)  
5'- GAA AGC TGA GAT GGA G -3' (FRAG 411) (SEQ ID NO:9790)  
5'- GAA AGC TGA GAT GGA -3' (FRAG 412) (SEQ ID NO:9791)  
5'- GAA AGC TGA GAT GG -3' (FRAG 413) (SEQ ID NO:9792)  
5'- GAA AGC TGA GAT G -3' (FRAG 414) (SEQ ID NO:9793)  
5'- GAA AGC TGA GAT -3' (FRAG 415) (SEQ ID NO:9794)  
5'- GAA AGC TGA GA-3' (FRAG 416) (SEQ ID NO:9795)  
5'- GAA AGC TGA G-3' (FRAG 417) (SEQ ID NO:9796)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 418) (SEQ ID NO:9797)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 419) (SEQ ID NO:9798)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 420) (SEQ ID NO:9799)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 421) (SEQ ID NO:9800)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 422) (SEQ ID NO:9801)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 423) (SEQ ID NO:9802)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 424) (SEQ ID NO:9803)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 425) (SEQ ID NO:9804)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 426) (SEQ ID NO:9805)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 427) (SEQ ID NO:9806)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 428) (SEQ ID NO:9807)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 429) (SEQ ID NO:9808)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 430) (SEQ ID NO:9809)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 431) (SEQ ID NO:9810)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 432) (SEQ ID NO:9811)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 433) (SEQ ID NO:9812)  
5'- AA AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 434) (SEQ ID NO:9813)  
5'- AA AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 435) (SEQ ID NO:9814)  
5'- AA AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 436) (SEQ ID NO:9815)  
5'- AA AGC TGA GAT GGA GGG CGG CA-3' (FRAG 437) (SEQ ID NO:9816)  
5'- AA AGC TGA GAT GGA GGG CGG C-3' (FRAG 438) (SEQ ID NO:9817)  
5'- AA AGC TGA GAT GGA GGG CGG -3' (FRAG 439) (SEQ ID NO:9818)  
5'- AA AGC TGA GAT GGA GGG CG -3' (FRAG 440) (SEQ ID NO:9819)  
5'- AA AGC TGA GAT GGA GGG C -3' (FRAG 441) (SEQ ID NO:9820)  
5'- AA AGC TGA GAT GGA GGG -3' (FRAG 442) (SEQ ID NO:9821)  
5'- AA AGC TGA GAT GGA GG -3' (FRAG 443) (SEQ ID NO:9822)  
5'- AA AGC TGA GAT GGA G -3' (FRAG 444) (SEQ ID NO:9823)  
5'- AA AGC TGA GAT GGA -3' (FRAG 445) (SEQ ID NO:9824)  
5'- AA AGC TGA GAT GG -3' (FRAG 446) (SEQ ID NO:9825)  
5'- AA AGC TGA GAT G -3' (FRAG 447) (SEQ ID NO:9826)  
5'- AA AGC TGA GAT -3' (FRAG 448) (SEQ ID NO:9827)  
5'- AA AGC TGA GA-3' (FRAG 449) (SEQ ID NO:9828)



- 5'- A AGC TGA GAT GGA GGG CG G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 450) (SEQ ID NO:9829)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 451) (SEQ ID NO:9830)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 452) (SEQ ID NO:9831)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 453) (SEQ ID NO:9832)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 454) (SEQ ID NO:9833)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 455) (SEQ ID NO:9834)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 456) (SEQ ID NO:9835)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 457) (SEQ ID NO:9836)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 458) (SEQ ID NO:9837)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 459) (SEQ ID NO:9838)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 460) (SEQ ID NO:9839)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 461) (SEQ ID NO:9840)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 462) (SEQ ID NO:9841)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 463) (SEQ ID NO:9842)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 464) (SEQ ID NO:9843)  
5'- A AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 465) (SEQ ID NO:9844)  
5'- A AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 466) (SEQ ID NO:9845)  
5'- A AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 467) (SEQ ID NO:9846)  
5'- A AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 468) (SEQ ID NO:9847)  
5'- A AGC TGA GAT GGA GGG CGG CA-3' (FRAG 469) (SEQ ID NO:9848)  
5'- A AGC TGA GAT GGA GGG CGG C-3' (FRAG 470) (SEQ ID NO:9849)  
5'- A AGC TGA GAT GGA GGG CGG -3' (FRAG 471) (SEQ ID NO:9850)  
5'- A AGC TGA GAT GGA GGG CG -3' (FRAG 472) (SEQ ID NO:9851)  
5'- A AGC TGA GAT GGA GGG C -3' (FRAG 473) (SEQ ID NO:9852)  
5'- A AGC TGA GAT GGA GGG -3' (FRAG 474) (SEQ ID NO:9853)  
5'- A AGC TGA GAT GGA GG -3' (FRAG 475) (SEQ ID NO:9854)  
5'- A AGC TGA GAT GGA G -3' (FRAG 476) (SEQ ID NO:9855)  
5'- A AGC TGA GAT GGA -3' (FRAG 477) (SEQ ID NO:9856)  
5'- A AGC TGA GAT GG -3' (FRAG 478) (SEQ ID NO:9857)  
5'- A AGC TGA GAT G -3' (FRAG 479) (SEQ ID NO:9858)  
5'- A AGC TGA GAT -3' (FRAG 480) (SEQ ID NO:9859)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 481) (SEQ ID NO:9860)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 482) (SEQ ID NO:9861)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 483) (SEQ ID NO:9862)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 484) (SEQ ID NO:9863)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 485) (SEQ ID NO:9864)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 486) (SEQ ID NO:9865)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 487) (SEQ ID NO:9866)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 488) (SEQ ID NO:9867)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 489) (SEQ ID NO:9868)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 490) (SEQ ID NO:9869)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 491) (SEQ ID NO:9870)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 492) (SEQ ID NO:9871)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 493) (SEQ ID NO:9872)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 494) (SEQ ID NO:9873)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 495) (SEQ ID NO:9874)  
5'- AGC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 496) (SEQ ID NO:9875)  
5'- AGC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 497) (SEQ ID NO:9876)  
5'- AGC TGA GAT GGA GGG CGG CAT G -3' (FRAG 498) (SEQ ID NO:9877)  
5'- AGC TGA GAT GGA GGG CGG CAT -3' (FRAG 499) (SEQ ID NO:9878)  
5'- AGC TGA GAT GGA GGG CGG CA-3' (FRAG 500) (SEQ ID NO:9879)  
5'- AGC TGA GAT GGA GGG CGG C-3' (FRAG 501) (SEQ ID NO:9880)  
5'- AGC TGA GAT GGA GGG CGG -3' (FRAG 502) (SEQ ID NO:9881)  
5'- AGC TGA GAT GGA GGG CG -3' (FRAG 503) (SEQ ID NO:9882)  
5'- AGC TGA GAT GGA GGG C -3' (FRAG 504) (SEQ ID NO:9883)  
5'- AGC TGA GAT GGA GGG -3' (FRAG 505) (SEQ ID NO:9884)  
5'- AGC TGA GAT GGA GG -3' (FRAG 506) (SEQ ID NO:9885)  
5'- AGC TGA GAT GGA G -3' (FRAG 507) (SEQ ID NO:9886)  
5'- AGC TGA GAT GGA -3' (FRAG 508) (SEQ ID NO:9887)  
5'- AGC TGA GAT GG -3' (FRAG 509) (SEQ ID NO:9888)  
5'- AGC TGA GAT G -3' (FRAG 510) (SEQ ID NO:9889)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 511) (SEQ ID NO:9890)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 512) (SEQ ID NO:9891)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 513) (SEQ ID NO:9892)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 514) (SEQ ID NO:9893)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 515) (SEQ ID NO:9894)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 516) (SEQ ID NO:9895)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 517) (SEQ ID NO:9896)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 518) (SEQ ID NO:9897)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 519) (SEQ ID NO:9898)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 520) (SEQ ID NO:9899)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 521) (SEQ ID NO:9900)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 522) (SEQ ID NO:9901)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 523) (SEQ ID NO:9902)  
5'- GC TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 524) (SEQ ID NO:9903)

- 5'- GC TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 525) (SEQ ID NO:9904)  
5'- GC TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 526) (SEQ ID NO:9905)  
5'- GC TGA GAT GGA GGG CGG CAT GG -3' (FRAG 527) (SEQ ID NO:9906)  
5'- GC TGA GAT GGA GGG CGG CAT G -3' (FRAG 528) (SEQ ID NO:9907)  
5 5'- GC TGA GAT GGA GGG CGG CAT -3' (FRAG 529) (SEQ ID NO:9908)  
5'- GC TGA GAT GGA GGG CGG CA-3' (FRAG 530) (SEQ ID NO:9909)  
5'- GC TGA GAT GGA GGG CGG C-3' (FRAG 531) (SEQ ID NO:9910)  
5'- GC TGA GAT GGA GGG CGG -3' (FRAG 532) (SEQ ID NO:9911)  
5'- GC TGA GAT GGA GGG CG -3' (FRAG 533) (SEQ ID NO:9912)  
10 5'- GC TGA GAT GGA GGG C -3' (FRAG 534) (SEQ ID NO:9913)  
5'- GC TGA GAT GGA GGG -3' (FRAG 535) (SEQ ID NO:9914)  
5'- GC TGA GAT GGA GG -3' (FRAG 536) (SEQ ID NO:9915)  
5'- GC TGA GAT GGA G -3' (FRAG 537) (SEQ ID NO:9916)  
5'- GC TGA GAT GGA -3' (FRAG 538) (SEQ ID NO:9917)  
15 5'- GC TGA GAT GG -3' (FRAG 539) (SEQ ID NO:9918)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 540) (SEQ ID NO:9919)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 541) (SEQ ID NO:9920)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 542) (SEQ ID NO:9921)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 543) (SEQ ID NO:9922)  
20 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 544) (SEQ ID NO:9923)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 545) (SEQ ID NO:9924)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 546) (SEQ ID NO:9925)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 547) (SEQ ID NO:9926)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 548) (SEQ ID NO:9927)  
25 5'- C TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 549) (SEQ ID NO:9928)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 550) (SEQ ID NO:9929)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 551) (SEQ ID NO:9930)  
5'- C TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 552) (SEQ ID NO:9931)  
5'- C TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 553) (SEQ ID NO:9932)  
30 5'- C TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 554) (SEQ ID NO:9933)  
5'- C TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 555) (SEQ ID NO:9934)  
5'- C TGA GAT GGA GGG CGG CAT GG -3' (FRAG 556) (SEQ ID NO:9935)  
5'- C TGA GAT GGA GGG CGG CAT G -3' (FRAG 557) (SEQ ID NO:9936)  
5'- C TGA GAT GGA GGG CGG CAT -3' (FRAG 558) (SEQ ID NO:9937)  
35 5'- C TGA GAT GGA GGG CGG CA-3' (FRAG 559) (SEQ ID NO:9938)  
5'- C TGA GAT GGA GGG CGG C-3' (FRAG 560) (SEQ ID NO:9939)  
5'- C TGA GAT GGA GGG CGG -3' (FRAG 561) (SEQ ID NO:9940)  
5'- C TGA GAT GGA GGG CG -3' (FRAG 562) (SEQ ID NO:9941)  
5'- C TGA GAT GGA GGG C -3' (FRAG 563) (SEQ ID NO:9942)  
40 5'- C TGA GAT GGA GGG -3' (FRAG 564) (SEQ ID NO:9943)  
5'- C TGA GAT GGA GG -3' (FRAG 565) (SEQ ID NO:9944)  
5'- C TGA GAT GGA G -3' (FRAG 566) (SEQ ID NO:9945)  
5'- C TGA GAT GGA -3' (FRAG 567) (SEQ ID NO:9946)  
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 568) (SEQ ID NO:9947)  
45 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 569) (SEQ ID NO:9948)  
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 570) (SEQ ID NO:9949)  
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 571) (SEQ ID NO:9950)  
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 572) (SEQ ID NO:9951)  
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 573) (SEQ ID NO:9952)  
50 5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 574) (SEQ ID NO:9953)  
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 575) (SEQ ID NO:9954)  
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 576) (SEQ ID NO:9955)  
5'- TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 577) (SEQ ID NO:9956)  
5'- TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 578) (SEQ ID NO:9957)  
55 5'- TGA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 579) (SEQ ID NO:9958)  
5'- TGA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 580) (SEQ ID NO:9959)  
5'- TGA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 581) (SEQ ID NO:9960)  
5'- TGA GAT GGA GGG CGG CAT GGC G-3' (FRAG 582) (SEQ ID NO:9961)  
5'- TGA GAT GGA GGG CGG CAT GGC -3' (FRAG 583) (SEQ ID NO:9962)  
60 5'- TGA GAT GGA GGG CGG CAT GG -3' (FRAG 584) (SEQ ID NO:9963)  
5'- TGA GAT GGA GGG CGG CAT G -3' (FRAG 585) (SEQ ID NO:9964)  
5'- TGA GAT GGA GGG CGG CAT -3' (FRAG 586) (SEQ ID NO:9965)  
5'- TGA GAT GGA GGG CGG CA-3' (FRAG 587) (SEQ ID NO:9966)  
5'- TGA GAT GGA GGG CGG C-3' (FRAG 588) (SEQ ID NO:9967)  
65 5'- TGA GAT GGA GGG CGG -3' (FRAG 589) (SEQ ID NO:9968)  
5'- TGA GAT GGA GGG CG -3' (FRAG 590) (SEQ ID NO:9969)  
5'- TGA GAT GGA GGG C -3' (FRAG 591) (SEQ ID NO:9970)  
5'- TGA GAT GGA GGG -3' (FRAG 592) (SEQ ID NO:9971)  
5'- TGA GAT GGA GG -3' (FRAG 593) (SEQ ID NO:9972)  
70 5'- TGA GAT GGA G -3' (FRAG 594) (SEQ ID NO:9973)  
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 595) (SEQ ID NO:9974)  
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 596) (SEQ ID NO:9975)  
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 597) (SEQ ID NO:9976)  
5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 598) (SEQ ID NO:9977)  
75 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 599) (SEQ ID NO:9978)

5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 600) (SEQ ID NO:9979)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 601) (SEQ ID NO:9980)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 602) (SEQ ID NO:9981)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 603) (SEQ ID NO:9982)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 604) (SEQ ID NO:9983)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 605) (SEQ ID NO:9984)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 606) (SEQ ID NO:9985)  
 5'- GA GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 607) (SEQ ID NO:9986)  
 5'- GA GAT GGA GGG CGG CAT GGC GG-3' (FRAG 608) (SEQ ID NO:9987)  
 10 5'- GA GAT GGA GGG CGG CAT GGC G-3' (FRAG 609) (SEQ ID NO:9988)  
 5'- GA GAT GGA GGG CGG CAT GGC -3' (FRAG 610) (SEQ ID NO:9989)  
 5'- GA GAT GGA GGG CGG CAT GG -3' (FRAG 611) (SEQ ID NO:9990)  
 5'- GA GAT GGA GGG CGG CAT G -3' (FRAG 612) (SEQ ID NO:9991)  
 5'- GA GAT GGA GGG CGG CAT -3' (FRAG 613) (SEQ ID NO:9992)  
 15 5'- GA GAT GGA GGG CGG CA-3' (FRAG 614) (SEQ ID NO:9993)  
 5'- GA GAT GGA GGG CGG C-3' (FRAG 615) (SEQ ID NO:9994)  
 5'- GA GAT GGA GGG CGG -3' (FRAG 616) (SEQ ID NO:9995)  
 5'- GA GAT GGA GGG CG -3' (FRAG 617) (SEQ ID NO:9996)  
 5'- GA GAT GGA GGG C -3' (FRAG 618) (SEQ ID NO:9997)  
 20 5'- GA GAT GGA GGG -3' (FRAG 619) (SEQ ID NO:9998)  
 5'- GA GAT GGA GG -3' (FRAG 620) (SEQ ID NO:9999)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 621) (SEQ ID NO:10000)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 622) (SEQ ID NO:10001)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 623) (SEQ ID NO:10002)  
 25 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 624) (SEQ ID NO:10003)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 625) (SEQ ID NO:10004)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 626) (SEQ ID NO:10005)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 627) (SEQ ID NO:10006)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 628) (SEQ ID NO:10007)  
 30 5'- A GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 629) (SEQ ID NO:10008)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 630) (SEQ ID NO:10009)  
 5'- A GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 631) (SEQ ID NO:10010)  
 5'- A GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 632) (SEQ ID NO:10011)  
 5'- A GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 633) (SEQ ID NO:10012)  
 35 5'- A GAT GGA GGG CGG CAT GGC GG-3' (FRAG 634) (SEQ ID NO:10013)  
 5'- A GAT GGA GGG CGG CAT GGC G-3' (FRAG 635) (SEQ ID NO:10014)  
 5'- A GAT GGA GGG CGG CAT GGC -3' (FRAG 636) (SEQ ID NO:10015)  
 5'- A GAT GGA GGG CGG CAT GG -3' (FRAG 637) (SEQ ID NO:10016)  
 5'- A GAT GGA GGG CGG CAT G -3' (FRAG 638) (SEQ ID NO:10017)  
 40 5'- A GAT GGA GGG CGG CAT -3' (FRAG 639) (SEQ ID NO:10018)  
 5'- A GAT GGA GGG CGG CA-3' (FRAG 640) (SEQ ID NO:10019)  
 5'- A GAT GGA GGG CGG C-3' (FRAG 641) (SEQ ID NO:10020)  
 5'- A GAT GGA GGG CGG -3' (FRAG 642) (SEQ ID NO:10021)  
 5'- A GAT GGA GGG CG -3' (FRAG 643) (SEQ ID NO:10022)  
 45 5'- A GAT GGA GGG C -3' (FRAG 644) (SEQ ID NO:10023)  
 5'- A GAT GGA GGG -3' (FRAG 645) (SEQ ID NO:10024)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 646) (SEQ ID NO:10025)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 647) (SEQ ID NO:10026)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 648) (SEQ ID NO:10027)  
 50 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 649) (SEQ ID NO:10028)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 650) (SEQ ID NO:10029)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 651) (SEQ ID NO:10030)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 652) (SEQ ID NO:10031)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 653) (SEQ ID NO:10032)  
 55 5'- GAT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 654) (SEQ ID NO:10033)  
 5'- GAT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 655) (SEQ ID NO:10034)  
 5'- GAT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 656) (SEQ ID NO:10035)  
 5'- GAT GGA GGG CGG CAT GGC GGG C-3' (FRAG 657) (SEQ ID NO:10036)  
 5'- GAT GGA GGG CGG CAT GGC GGG -3' (FRAG 658) (SEQ ID NO:10037)  
 60 5'- GAT GGA GGG CGG CAT GGC GG-3' (FRAG 659) (SEQ ID NO:10038)  
 5'- GAT GGA GGG CGG CAT GGC G-3' (FRAG 660) (SEQ ID NO:10039)  
 5'- GAT GGA GGG CGG CAT GGC -3' (FRAG 661) (SEQ ID NO:10040)  
 5'- GAT GGA GGG CGG CAT GG -3' (FRAG 662) (SEQ ID NO:10041)  
 5'- GAT GGA GGG CGG CAT G -3' (FRAG 663) (SEQ ID NO:10042)  
 65 5'- GAT GGA GGG CGG CAT -3' (FRAG 664) (SEQ ID NO:10043)  
 5'- GAT GGA GGG CGG CA-3' (FRAG 665) (SEQ ID NO:10044)  
 5'- GAT GGA GGG CGG C-3' (FRAG 666) (SEQ ID NO:10045)  
 5'- GAT GGA GGG CGG -3' (FRAG 667) (SEQ ID NO:10046)  
 5'- GAT GGA GGG CG -3' (FRAG 668) (SEQ ID NO:10047)  
 70 5'- GAT GGA GGG C -3' (FRAG 669) (SEQ ID NO:10048)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 670) (SEQ ID NO:10049)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 671) (SEQ ID NO:10050)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 672) (SEQ ID NO:10051)  
 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 673) (SEQ ID NO:10052)  
 75 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 674) (SEQ ID NO:10053)

- 5'- AT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 675) (SEQ ID NO:10054)  
5'- AT GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 676) (SEQ ID NO:10055)  
5'- AT GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 677) (SEQ ID NO:10056)  
5'- AT GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 678) (SEQ ID NO:10057)  
5'- AT GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 679) (SEQ ID NO:10058)  
5'- AT GGA GGG CGG CAT GGC GGG CA-3' (FRAG 680) (SEQ ID NO:10059)  
5'- AT GGA GGG CGG CAT GGC GGG C-3' (FRAG 681) (SEQ ID NO:10060)  
5'- AT GGA GGG CGG CAT GGC GGG -3' (FRAG 682) (SEQ ID NO:10061)  
5'- AT GGA GGG CGG CAT GGC GG-3' (FRAG 683) (SEQ ID NO:10062)  
5'- AT GGA GGG CGG CAT GGC G-3' (FRAG 684) (SEQ ID NO:10063)  
5'- AT GGA GGG CGG CAT GGC -3' (FRAG 685) (SEQ ID NO:10064)  
5'- AT GGA GGG CGG CAT GG -3' (FRAG 686) (SEQ ID NO:10065)  
5'- AT GGA GGG CGG CAT G -3' (FRAG 687) (SEQ ID NO:10066)  
5'- AT GGA GGG CGG CAT -3' (FRAG 688) (SEQ ID NO:10067)  
5'- AT GGA GGG CGG CA-3' (FRAG 689) (SEQ ID NO:10068)  
5'- AT GGA GGG CGG C-3' (FRAG 690) (SEQ ID NO:10069)  
5'- AT GGA GGG CGG -3' (FRAG 691) (SEQ ID NO:10070)  
5'- AT GGA GGG CG -3' (FRAG 692) (SEQ ID NO:10071)  
5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 693) (SEQ ID NO:10072)  
5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 694) (SEQ ID NO:10073)  
5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 695) (SEQ ID NO:10074)  
5'- T GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 696) (SEQ ID NO:10075)  
5'- T GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 697) (SEQ ID NO:10076)  
5'- T GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 698) (SEQ ID NO:10077)  
5'- T GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 699) (SEQ ID NO:10078)  
5'- T GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 700) (SEQ ID NO:10079)  
5'- T GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 701) (SEQ ID NO:10080)  
5'- T GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 702) (SEQ ID NO:10081)  
5'- T GGA GGG CGG CAT GGC GGG CA-3' (FRAG 703) (SEQ ID NO:10082)  
5'- T GGA GGG CGG CAT GGC GGG C-3' (FRAG 704) (SEQ ID NO:10083)  
5'- T GGA GGG CGG CAT GGC GGG -3' (FRAG 705) (SEQ ID NO:10084)  
5'- T GGA GGG CGG CAT GGC GG-3' (FRAG 706) (SEQ ID NO:10085)  
5'- T GGA GGG CGG CAT GGC G-3' (FRAG 707) (SEQ ID NO:10086)  
5'- T GGA GGG CGG CAT GGC -3' (FRAG 708) (SEQ ID NO:10087)  
5'- T GGA GGG CGG CAT GG -3' (FRAG 709) (SEQ ID NO:10088)  
5'- T GGA GGG CGG CAT G -3' (FRAG 710) (SEQ ID NO:10089)  
5'- T GGA GGG CGG CAT -3' (FRAG 711) (SEQ ID NO:10090)  
5'- T GGA GGG CGG CA-3' (FRAG 712) (SEQ ID NO:10091)  
5'- T GGA GGG CGG C-3' (FRAG 713) (SEQ ID NO:10092)  
5'- T GGA GGG CGG -3' (FRAG 714) (SEQ ID NO:10093)  
5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 715) (SEQ ID NO:10094)  
5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 716) (SEQ ID NO:10095)  
5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 717) (SEQ ID NO:10096)  
5'- GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 718) (SEQ ID NO:10097)  
5'- GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 719) (SEQ ID NO:10098)  
5'- GGA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 720) (SEQ ID NO:10099)  
5'- GGA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 721) (SEQ ID NO:10100)  
5'- GGA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 722) (SEQ ID NO:10101)  
5'- GGA GGG CGG CAT GGC GGG CAC A-3' (FRAG 723) (SEQ ID NO:10102)  
5'- GGA GGG CGG CAT GGC GGG CAC-3' (FRAG 724) (SEQ ID NO:10103)  
5'- GGA GGG CGG CAT GGC GGG CA-3' (FRAG 725) (SEQ ID NO:10104)  
5'- GGA GGG CGG CAT GGC GGG C-3' (FRAG 726) (SEQ ID NO:10105)  
5'- GGA GGG CGG CAT GGC GGG -3' (FRAG 727) (SEQ ID NO:10106)  
5'- GGA GGG CGG CAT GGC GG-3' (FRAG 728) (SEQ ID NO:10107)  
5'- GGA GGG CGG CAT GGC G-3' (FRAG 729) (SEQ ID NO:10108)  
5'- GGA GGG CGG CAT GGC -3' (FRAG 730) (SEQ ID NO:10109)  
5'- GGA GGG CGG CAT GG -3' (FRAG 731) (SEQ ID NO:10110)  
5'- GGA GGG CGG CAT G -3' (FRAG 732) (SEQ ID NO:10111)  
5'- GGA GGG CGG CAT -3' (FRAG 733) (SEQ ID NO:10112)  
5'- GGA GGG CGG CA-3' (FRAG 734) (SEQ ID NO:10113)  
5'- GGA GGG CGG C-3' (FRAG 735) (SEQ ID NO:10114)  
5'- GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 736) (SEQ ID NO:10115)  
5'- GA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 737) (SEQ ID NO:10116)  
5'- GA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 738) (SEQ ID NO:10117)  
5'- GA GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 739) (SEQ ID NO:10118)  
5'- GA GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 740) (SEQ ID NO:10119)  
5'- GA GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 741) (SEQ ID NO:10120)  
5'- GA GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 742) (SEQ ID NO:10121)  
5'- GA GGG CGG CAT GGC GGG CAC AG-3' (FRAG 743) (SEQ ID NO:10122)  
5'- GA GGG CGG CAT GGC GGG CAC A-3' (FRAG 744) (SEQ ID NO:10123)  
5'- GA GGG CGG CAT GGC GGG CAC-3' (FRAG 745) (SEQ ID NO:10124)  
5'- GA GGG CGG CAT GGC GGG CA-3' (FRAG 746) (SEQ ID NO:10125)  
5'- GA GGG CGG CAT GGC GGG C-3' (FRAG 747) (SEQ ID NO:10126)  
5'- GA GGG CGG CAT GGC GGG -3' (FRAG 748) (SEQ ID NO:10127)  
5'- GA GGG CGG CAT GGC GG-3' (FRAG 749) (SEQ ID NO:10128)

5'-	GA GGG CGG CAT GGC G-3' (FRAG 750) (SEQ ID NO:10129)
5'-	GA GGG CGG CAT GGC -3' (FRAG 751) (SEQ ID NO:10130)
5'-	GA GGG CGG CAT GG -3' (FRAG 752) (SEQ ID NO:10131)
5'-	GA GGG CGG CAT G -3' (FRAG 753) (SEQ ID NO:10132)
5	5'- GA GGG CGG CAT -3' (FRAG 754) (SEQ ID NO:10133)
5'-	GA GGG CGG CA-3' (FRAG 755) (SEQ ID NO:10134)
5'-	A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 756) (SEQ ID NO:10135)
5'-	A GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 757) (SEQ ID NO:10136)
5'-	A GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 758) (SEQ ID NO:10137)
10	5'- A GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 759) (SEQ ID NO:10138)
5'-	A GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 760) (SEQ ID NO:10139)
5'-	A GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 761) (SEQ ID NO:10140)
5'-	A GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 762) (SEQ ID NO:10141)
5'-	A GGG CGG CAT GGC GGG CAC AG-3' (FRAG 763) (SEQ ID NO:10142)
15	5'- A GGG CGG CAT GGC GGG CAC A-3' (FRAG 764) (SEQ ID NO:10143)
5'-	A GGG CGG CAT GGC GGG CAC-3' (FRAG 765) (SEQ ID NO:10144)
5'-	A GGG CGG CAT GGC GGG CA-3' (FRAG 766) (SEQ ID NO:10145)
5'-	A GGG CGG CAT GGC GGG C-3' (FRAG 767) (SEQ ID NO:10146)
5'-	A GGG CGG CAT GGC GGG -3' (FRAG 768) (SEQ ID NO:10147)
20	5'- A GGG CGG CAT GGC GG-3' (FRAG 769) (SEQ ID NO:10148)
5'-	A GGG CGG CAT GGC G-3' (FRAG 770) (SEQ ID NO:10149)
5'-	A GGG CGG CAT GGC -3' (FRAG 771) (SEQ ID NO:10150)
5'-	A GGG CGG CAT GG -3' (FRAG 772) (SEQ ID NO:10151)
5'-	A GGG CGG CAT G -3' (FRAG 773) (SEQ ID NO:10152)
25	5'- A GGG CGG CAT -3' (FRAG 774) (SEQ ID NO:10153)
5'-	GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 775) (SEQ ID NO:10154)
5'-	GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 776) (SEQ ID NO:10155)
5'-	GGG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 777) (SEQ ID NO:10156)
5'-	GGG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 778) (SEQ ID NO:10157)
30	5'- GGG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 779) (SEQ ID NO:10158)
5'-	GGG CGG CAT GGC GGG CAC AGG C-3' (FRAG 780) (SEQ ID NO:10159)
5'-	GGG CGG CAT GGC GGG CAC AGG -3' (FRAG 781) (SEQ ID NO:10160)
5'-	GGG CGG CAT GGC GGG CAC AG-3' (FRAG 782) (SEQ ID NO:10161)
5'-	GGG CGG CAT GGC GGG CAC A-3' (FRAG 783) (SEQ ID NO:10162)
35	5'- GGG CGG CAT GGC GGG CAC-3' (FRAG 784) (SEQ ID NO:10163)
5'-	GGG CGG CAT GGC GGG CA-3' (FRAG 785) (SEQ ID NO:10164)
5'-	GGG CGG CAT GGC GGG C-3' (FRAG 786) (SEQ ID NO:10165)
5'-	GGG CGG CAT GGC GGG -3' (FRAG 787) (SEQ ID NO:10166)
5'-	GGG CGG CAT GGC GG-3' (FRAG 788) (SEQ ID NO:10167)
40	5'- GGG CGG CAT GGC G-3' (FRAG 789) (SEQ ID NO:10168)
5'-	GGG CGG CAT GGC -3' (FRAG 790) (SEQ ID NO:10169)
5'-	GGG CGG CAT GG -3' (FRAG 791) (SEQ ID NO:10170)
5'-	GGG CGG CAT G -3' (FRAG 792) (SEQ ID NO:10171)
5'-	GG CGG CAT GGC GGG CAC AG G CTG GGC-3' (FRAG 793) (SEQ ID NO:10172)
45	5'- GG CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 794) (SEQ ID NO:10173)
5'-	GG CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 795) (SEQ ID NO:10174)
5'-	GG CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 796) (SEQ ID NO:10175)
5'-	GG CGG CAT GGC GGG CAC AGG CT-3' (FRAG 797) (SEQ ID NO:10176)
5'-	GG CGG CAT GGC GGG CAC AGG C-3' (FRAG 798) (SEQ ID NO:10177)
50	5'- GG CGG CAT GGC GGG CAC AGG -3' (FRAG 799) (SEQ ID NO:10178)
5'-	GG CGG CAT GGC GGG CAC AG-3' (FRAG 800) (SEQ ID NO:10179)
5'-	GG CGG CAT GGC GGG CAC A-3' (FRAG 801) (SEQ ID NO:10180)
5'-	GG CGG CAT GGC GGG CAC-3' (FRAG 802) (SEQ ID NO:10181)
5'-	GG CGG CAT GGC GGG CA-3' (FRAG 803) (SEQ ID NO:10182)
55	5'- GG CGG CAT GGC GGG C-3' (FRAG 804) (SEQ ID NO:10183)
5'-	GG CGG CAT GGC GGG -3' (FRAG 805) (SEQ ID NO:10184)
5'-	GG CGG CAT GGC GG-3' (FRAG 806) (SEQ ID NO:10185)
5'-	GG CGG CAT GGC G-3' (FRAG 807) (SEQ ID NO:10186)
5'-	GG CGG CAT GGC -3' (FRAG 808) (SEQ ID NO:10187)
60	5'- GG CGG CAT GG -3' (FRAG 809) (SEQ ID NO:10188)
5'-	G CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 810) (SEQ ID NO:10189)
5'-	G CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 811) (SEQ ID NO:10190)
5'-	G CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 812) (SEQ ID NO:10191)
5'-	G CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 813) (SEQ ID NO:10192)
65	5'- G CGG CAT GGC GGG CAC AGG CT-3' (FRAG 814) (SEQ ID NO:10193)
5'-	G CGG CAT GGC GGG CAC AGG C-3' (FRAG 815) (SEQ ID NO:10194)
5'-	G CGG CAT GGC GGG CAC AGG -3' (FRAG 816) (SEQ ID NO:10195)
5'-	G CGG CAT GGC GGG CAC AG-3' (FRAG 817) (SEQ ID NO:10196)
5'-	G CGG CAT GGC GGG CAC A-3' (FRAG 818) (SEQ ID NO:10197)
70	5'- G CGG CAT GGC GGG CAC-3' (FRAG 819) (SEQ ID NO:10198)
5'-	G CGG CAT GGC GGG CA-3' (FRAG 820) (SEQ ID NO:10199)
5'-	G CGG CAT GGC GGG C-3' (FRAG 821) (SEQ ID NO:10200)
5'-	G CGG CAT GGC GGG -3' (FRAG 822) (SEQ ID NO:10201)
5'-	G CGG CAT GGC GG-3' (FRAG 823) (SEQ ID NO:10202)
75	5'- G CGG CAT GGC G-3' (FRAG 824) (SEQ ID NO:10203)

5'- G CGG CAT GGC -3' (FRAG 825) (SEQ ID NO:10204)  
5'- CGG CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 826) (SEQ ID NO:10205)  
5'- CGG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 827) (SEQ ID NO:10206)  
5'- CGG CAT GGC GGG CAC AGG CTG G-3' (FRAG 828) (SEQ ID NO:10207)  
5 5'- CGG CAT GGC GGG CAC AGG CTG -3' (FRAG 829) (SEQ ID NO:10208)  
5'- CGG CAT GGC GGG CAC AGG CT-3' (FRAG 830) (SEQ ID NO:10209)  
5'- CGG CAT GGC GGG CAC AGG C-3' (FRAG 831) (SEQ ID NO:10210)  
5'- CGG CAT GGC GGG CAC AGG -3' (FRAG 832) (SEQ ID NO:10211)  
5'- CGG CAT GGC GGG CAC AG-3' (FRAG 833) (SEQ ID NO:10212)  
10 5'- CGG CAT GGC GGG CAC A-3' (FRAG 834) (SEQ ID NO:10213)  
5'- CGG CAT GGC GGG CAC-3' (FRAG 835) (SEQ ID NO:10214)  
5'- CGG CAT GGC GGG CA-3' (FRAG 836) (SEQ ID NO:10215)  
5'- CGG CAT GGC GGG C-3' (FRAG 837) (SEQ ID NO:10216)  
5'- CGG CAT GGC GGG -3' (FRAG 838) (SEQ ID NO:10217)  
15 5'- CGG CAT GGC GG-3' (FRAG 839) (SEQ ID NO:10218)  
5'- CGG CAT GGC G-3' (FRAG 840) (SEQ ID NO:10219)  
5'- GG CAT GGC GGG CAC AGG C TG GGC-3' (FRAG 841) (SEQ ID NO:10220)  
5'- GG CAT GGC GGG CAC AGG CTG GG-3' (FRAG 842) (SEQ ID NO:10221)  
5'- GG CAT GGC GGG CAC AGG CTG G-3' (FRAG 843) (SEQ ID NO:10222)  
20 5'- GG CAT GGC GGG CAC AGG CTG -3' (FRAG 844) (SEQ ID NO:10223)  
5'- GG CAT GGC GGG CAC AGG CT-3' (FRAG 845) (SEQ ID NO:10224)  
5'- GG CAT GGC GGG CAC AGG C-3' (FRAG 846) (SEQ ID NO:10225)  
5'- GG CAT GGC GGG CAC AGG -3' (FRAG 847) (SEQ ID NO:10226)  
5'- GG CAT GGC GGG CAC AG-3' (FRAG 848) (SEQ ID NO:10227)  
25 5'- GG CAT GGC GGG CAC A-3' (FRAG 849) (SEQ ID NO:10228)  
5'- GG CAT GGC GGG CAC-3' (FRAG 850) (SEQ ID NO:10229)  
5'- GG CAT GGC GGG CA-3' (FRAG 851) (SEQ ID NO:10230)  
5'- GG CAT GGC GGG C-3' (FRAG 852) (SEQ ID NO:10231)  
5'- GG CAT GGC GGG -3' (FRAG 853) (SEQ ID NO:10232)  
30 5'- GG CAT GGC GG-3' (FRAG 854) (SEQ ID NO:10233)  
5'- G CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 855) (SEQ ID NO:10234)  
5'- G CAT GGC GGG CAC AGG CTG GG-3' (FRAG 856) (SEQ ID NO:10235)  
5'- G CAT GGC GGG CAC AGG CTG G-3' (FRAG 857) (SEQ ID NO:10236)  
5'- G CAT GGC GGG CAC AGG CTG -3' (FRAG 858) (SEQ ID NO:10237)  
35 5'- G CAT GGC GGG CAC AGG CT-3' (FRAG 859) (SEQ ID NO:10238)  
5'- G CAT GGC GGG CAC AGG C-3' (FRAG 860) (SEQ ID NO:10239)  
5'- G CAT GGC GGG CAC AGG -3' (FRAG 861) (SEQ ID NO:10240)  
5'- G CAT GGC GGG CAC AG-3' (FRAG 862) (SEQ ID NO:10241)  
5'- G CAT GGC GGG CAC A-3' (FRAG 863) (SEQ ID NO:10242)  
40 5'- G CAT GGC GGG CAC-3' (FRAG 864) (SEQ ID NO:10243)  
5'- G CAT GGC GGG CA-3' (FRAG 865) (SEQ ID NO:10244)  
5'- G CAT GGC GGG C-3' (FRAG 866) (SEQ ID NO:10245)  
5'- G CAT GGC GGG -3' (FRAG 867) (SEQ ID NO:10246)  
5'- CAT GGC GGG CAC AGG CTG GGC-3' (FRAG 868) (SEQ ID NO:10247)  
45 5'- CAT GGC GGG CAC AGG CTG GG-3' (FRAG 869) (SEQ ID NO:10248)  
5'- CAT GGC GGG CAC AGG CTG G-3' (FRAG 870) (SEQ ID NO:10249)  
5'- CAT GGC GGG CAC AGG CTG -3' (FRAG 871) (SEQ ID NO:10250)  
5'- CAT GGC GGG CAC AGG CT-3' (FRAG 872) (SEQ ID NO:10251)  
5'- CAT GGC GGG CAC AGG C-3' (FRAG 873) (SEQ ID NO:10252)  
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5'- CAT GGC GGG CAC A-3' (FRAG 876) (SEQ ID NO:10255)  
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55 5'- CAT GGC GGG C-3' (FRAG 879) (SEQ ID NO:10258)  
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5'- AT GGC GGG CAC AGG CTG GG-3' (FRAG 881) (SEQ ID NO:10260)  
5'- AT GGC GGG CAC AGG CTG G-3' (FRAG 882) (SEQ ID NO:10261)  
5'- AT GGC GGG CAC AGG CTG -3' (FRAG 883) (SEQ ID NO:10262)  
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5'- AT GGC GGG CAC AG-3' (FRAG 887) (SEQ ID NO:10266)  
5'- AT GGC GGG CAC A-3' (FRAG 888) (SEQ ID NO:10267)  
65 5'- AT GGC GGG CAC-3' (FRAG 889) (SEQ ID NO:10268)  
5'- AT GGC GGG CA-3' (FRAG 890) (SEQ ID NO:10269)  
5'- T GGC GGG CAC AGG CTG GGC-3' (FRAG 891) (SEQ ID NO:10270)  
5'- T GGC GGG CAC AGG CTG GG-3' (FRAG 892) (SEQ ID NO:10271)  
5'- T GGC GGG CAC AGG CTG G-3' (FRAG 893) (SEQ ID NO:10272)  
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5'- T GGC GGG CAC AGG C-3' (FRAG 896) (SEQ ID NO:10275)  
5'- T GGC GGG CAC AGG -3' (FRAG 897) (SEQ ID NO:10276)  
5'- T GGC GGG CAC AG-3' (FRAG 898) (SEQ ID NO:10277)  
75 5'- T GGC GGG CAC A-3' (FRAG 899) (SEQ ID NO:10278)



- 5'- T GGC GGG CAC -3' (FRAG 900) (SEQ ID NO:10279)  
 5'- GGC GGG CAC AGG CTG GGC -3' (FRAG 901) (SEQ ID NO:10280)  
 5'- GGC GGG CAC AGG CTG GG -3' (FRAG 902) (SEQ ID NO:10281)  
 5'- GGC GGG CAC AGG CTG G -3' (FRAG 903) (SEQ ID NO:10282)  
 5 GGC GGG CAC AGG CTG -3' (FRAG 904) (SEQ ID NO:10283)  
 5'- GGC GGG CAC AGG CT -3' (FRAG 905) (SEQ ID NO:10284)  
 5'- GGC GGG CAC AGG C -3' (FRAG 906) (SEQ ID NO:10285)  
 5'- GGC GGG CAC AGG -3' (FRAG 907) (SEQ ID NO:10286)  
 5'- GGC GGG CAC AG -3' (FRAG 908) (SEQ ID NO:10287)  
 10 5'- GGC GGG CAC A -3' (FRAG 909) (SEQ ID NO:10288)  
 5'- GC GGG CAC AGG CTG GGC -3' (FRAG 910) (SEQ ID NO:10289)  
 5'- GC GGG CAC AGG CTG GG -3' (FRAG 911) (SEQ ID NO:10290)  
 5'- GC GGG CAC AGG CTG G -3' (FRAG 912) (SEQ ID NO:10291)  
 5'- GC GGG CAC AGG CTG -3' (FRAG 913) (SEQ ID NO:10292)  
 15 5'- GC GGG CAC AGG CT -3' (FRAG 914) (SEQ ID NO:10293)  
 5'- GC GGG CAC AGG C -3' (FRAG 915) (SEQ ID NO:10294)  
 5'- GC GGG CAC AGG -3' (FRAG 916) (SEQ ID NO:10295)  
 5'- GC GGG CAC AG -3' (FRAG 917) (SEQ ID NO:10296)  
 5'- C GGG CAC AGG CTG GGC -3' (FRAG 918) (SEQ ID NO:10297)  
 20 5'- GGG CAC AGG CTG GG -3' (FRAG 919) (SEQ ID NO:10298)  
 5'- C GGG CAC AGG CTG G -3' (FRAG 920) (SEQ ID NO:10299)  
 5'- C GGG CAC AGG CTG -3' (FRAG 921) (SEQ ID NO:10300)  
 5'- C GGG CAC AGG CT -3' (FRAG 922) (SEQ ID NO:10301)  
 5'- C GGG CAC AGG C -3' (FRAG 923) (SEQ ID NO:10302)  
 25 5'- C GGG CAC AGG -3' (FRAG 924) (SEQ ID NO:10303)  
 5'- GGG CAC AGG CTG GGC -3' (FRAG 925) (SEQ ID NO:10304)  
 5'- GGG CAC AGG CTG GG -3' (FRAG 926) (SEQ ID NO:10305)  
 5'- GGG CAC AGG CTG G -3' (FRAG 927) (SEQ ID NO:10306)  
 5'- GGG CAC AGG CTG -3' (FRAG 928) (SEQ ID NO:10307)  
 30 5'- GGG CAC AGG CT -3' (FRAG 929) (SEQ ID NO:10308)  
 5'- GGG CAC AGG C -3' (FRAG 930) (SEQ ID NO:10309)  
 5'- GG CAC AGG CTG GGC -3' (FRAG 931) (SEQ ID NO:10310)  
 5'- GG CAC AGG CTG GG -3' (FRAG 932) (SEQ ID NO:10311)  
 5'- GG CAC AGG CTG G -3' (FRAG 933) (SEQ ID NO:10312)  
 35 5'- GG CAC AGG CTG -3' (FRAG 934) (SEQ ID NO:10313)  
 5'- GG CAC AGG CT -3' (FRAG 935) (SEQ ID NO:10314)  
 5'- G CAC AGG CTG GGC -3' (FRAG 936) (SEQ ID NO:10315)  
 5'- G CAC AGG CTG GG -3' (FRAG 937) (SEQ ID NO:10316)  
 5'- G CAC AGG CTG G -3' (FRAG 938) (SEQ ID NO:10317)  
 40 5'- G CAC AGG CTG -3' (FRAG 939) (SEQ ID NO:10318)  
 5'- CAC AGG CTG GGC -3' (FRAG 940) (SEQ ID NO:10319)  
 5'- CAC AGG CTG GG -3' (FRAG 941) (SEQ ID NO:10320)  
 5'- CAC AGG CTG G -3' (FRAG 942) (SEQ ID NO:10321)  
 5'- AC AGG CTG GGC -3' (FRAG 943) (SEQ ID NO:10322)  
 45 5'- AC AGG CTG GG -3' (FRAG 944) (SEQ ID NO:10323)  
 5'- C AGG CTG GGC -3' (FRAG 945) (SEQ ID NO:10324)  
 5'- TTT TCC TTC CTT TGT CTC TCT TC (FRAG 946) (SEQ ID NO:10325)  
 5'- GCT CCC GGC TGC CTG (FRAG 947) (SEQ ID NO:10326)  
 5'- CTC GGC CGT GCG GCT CTG TCG CTC CCG GT (FRAG 948) (SEQ ID NO:10327)  
 50 5'- CCG CCG CCC TCC GGG GGG TC (FRAG 949) (SEQ ID NO:10328)  
 5'- TGC TGC CGT TGG CTG CCC (FRAG 950) (SEQ ID NO:10329)  
 5'- CTT CTG CGG GTC GCC GG (FRAG 951) (SEQ ID NO:10330)  
 5'- TGC TGG GCT TGT GGC (FRAG 952) (SEQ ID NO:10331)  
 5'- GGC CTC TCT TCT GGG (FRAG 953) (SEQ ID NO:10332)  
 55 5'- CCT GGT CCC TCC GT (FRAG 954) (SEQ ID NO:10333)  
 5'- GGT GGC TCC TCT GC (FRAG 955) (SEQ ID NO:10334)  
 5'- GCT TGG TCC TGG GGC TGC (FRAG 956) (SEQ ID NO:10335)  
 5'- TGC TCT CCT CTC CTT (FRAG 957) (SEQ ID NO:10336)
- Human Adenosine A2a Receptor Nucleic Acid and Antisense Oligonucleotide Fragments**
- 60 5'- TGC TTT TCT TTT CTG GGC CTC TGT GGT CTG TTT TTT TCT G GCC CTG CTG GGG CGC TCT CC GCC GCC CGC CTG GCT  
 CCC GGB GCC CBT GBT GGG CBT GCC GTG GTT CTT GCC CTC CTT TGG CTG CCG TGC CCG CTC CCC GGC CTC CTG GCG GGT  
 GGC CGT TG GGC CCG TGT TCC CCT GGG -GCC TGG GGC TCC CTT CTC TC GCC CTT CTT GCT GGG CCT C TGC TGC TGC TGG  
 TGC TGT GGC CCC C GTA CAC CGA GGA GCC CAT GAT GGG CAT GCC ACA GAC GAC AGG C GTB CBC CGB GGB GCC CBT  
 GBT GGG CBT GCC BCB GBC GBC BGG C -3' (FRAG NO. 1665) (SEQ ID NO:11049)  
 65 5'- CTG GGC CTC -3' (FRAG 1666) (SEQ ID NO:11050)  
 5'- TGC TTT TCT TTT CTG GGC CTC -3' (FRAG 958) (SEQ ID NO:10337)  
 5'- TGT GGT CTG TTT TTT TCT G -3' (FRAG 959) (SEQ ID NO:10338)  
 5'- GCC CTG CTG GGG CGC TCT CC -3' (FRAG 960) (SEQ ID NO:10339)  
 5'- GCC GCC CGC CTG GCT CCC -3' (FRAG 961) (SEQ ID NO:10340)  
 70 5'- GGB GCC CBT GBT GGG CBT GCC -3' (FRAG 962) (SEQ ID NO:10341)  
 5'- GTG GTT CTT GCC CTC CTT TGG CTG -3' (FRAG 963) (SEQ ID NO:10342)  
 5'- CCG TGC CCG CTC CCC GGC -3' (FRAG 964) (SEQ ID NO:10343)  
 5'- CTC CTG GCG GGT GGC CGT TG -3' (FRAG 965) (SEQ ID NO:10344)  
 5'- GGC CCG TGT TCC CCT GGG -3' (FRAG 966) (SEQ ID NO:10345)  
 75 5'- GCC TGG GGC TCC CTT CTC TC -3' (FRAG 967) (SEQ ID NO:10346)

5'-GCC CTT CTT GCT GGG CCT C-3' (FRAG 968) (SEQ ID NO:10347)

5'-TGC TGC TGC TGG TGC TGT GGC CCC C-3' (FRAG 969) (SEQ ID NO:10348)

5'-GTACACCGAGGAGCCATGATGGGCATGCCACAGACGACAGGC-3' (FRAG 970) (SEQ ID NO:10349)

5'-GTBCBCCGGBGBCCBTGBTGCGCBTGCBCBGBCBGBCBGGC-3' (FRAG 971) (SEQ ID NO:10350)

**5 Human Adenosine A2b Receptor Nucleic Acid & Antisense Oligonucleotide Fragments**

5'-GGC GCC GTG CCG CGT CTT GGT GGC GGC GG GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC GTT CGC GCC CGC GCG  
 GGG CCC CTC CGG TCC CGG GTC GGG GCC CCC CGC GGC C GCC TCG GGG CTG GGG CGC TGG TGG CCG GG CCG CGC CTC  
 CGC CTG CCG CTT CTG GCT GGG CCC CGG GCG CCC CCT CCC CTC TTG CTC GGG TCC CCG TG ACA GCG CGT CCT GTG TCT  
 CCA GCA GCA TGG CCG GGC CAG CTG GGC CCC BCB GCG CGT CCT GTG TCT CCB GCB GCB TGG CCG GGC CBG CTG GGC  
 10 CCC CCCAGCCCCG AGGCTCAGAA GCGGCAGGCG GAGGCGCGGT CCGGGCGCTA TGGCCATGCC CGGCGGGTCT  
 CACGCGGCTG CCCCTCGCCC GCGCGCCTT CGGTAGGGGG CGCCCCGGGC CCAGCTGGCC CGGCCATGCT GCTGGAGACA  
 CAGGACGCGC TGTACGTGGC GCTGGAGCTG GTCATCGCCG CGCTTTCGGT GCGGGGCAAC GTGCTGGTGT GCGCCGCGGT  
 GGGCACGGCG AACACTCTGC AGACGCCAC CAACTACTTC CTGGTGTCCC TGGCTGCGGC CGACGTGGCC GTGGGGTCT  
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 15 CTGTGTCTCA CGCAGAGCTC CATCTTCAGC CTCTGCGCG TGCGAGTCGA CAGATACCTG GCCATCTGTG TCCGCTCAG  
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 TCCCATTTCT GGGGTGGAAC AGTAAAGACA GTGCCACCAA CAACTGCACA GAACCTGGG ATGGAACCA GAATGAAAGC  
 TGCTGCCTTG TGAAGTGTCT CTGTGAAAT GTGGTCCCA TGAGCTACAT GGTATATTTC AATTTCTTTT GGTGTGTCT  
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 25 ACGGTGCGTT TTCACTGTGA AAGATAGCTA CACCTCACAA GGAATGGAG TGCCTCTCTT GAGCACTTCC CTGAGCTAC  
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 30 GGCATGTGGT GTACACCTG TAATTCCAGC ACTTTGGGAG GCCAAGGCAG GCGGATCACG AGGTGAGGAG TTCAAAACCA  
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45 TGACGTGGC GCTGGAGCTG GTCATCGCG CGCTTTCGCT GCGCGGCAAC GTGCTGGTGT GCGCCGCGGT GGGCACGGCG  
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75 CCCTGGGATG GAACACAGAA TGAAAGCTGC TGCCTTGTGA AGTGTCTCTT TGAGAATGTG GTCCCCATGA GCTACATGGT

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 35 5'-GCT GGG CCC CGG-3' (FRAG. NO: 1672) (SEQ ID NO:11056)  
 5'-CGG GTC GGG GCC CCC C-3' (FRAG. NO: 1673) (SEQ ID NO:11057)  
 5'-CGC GCC CGC G-3' (FRAG. NO: 1674) (SEQ ID NO:11058)  
 5'-GGC GCC GTG CCG CGT CTT GGT GGC GGC GG-3' (FRAG 972) (SEQ ID NO:10351)  
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 40 5'-GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC-3' (FRAG 974) (SEQ ID NO:10353)  
 5'-CGG GTC GGG GCC CCC CGC GGC C-3' (FRAG 975) (SEQ ID NO:10354)  
 5'-GCC TCG GGG CTG GGG CGC TGG TGG CCG GG-3' (FRAG 976) (SEQ ID NO:10355)  
 5'-CCG CGC CTC CGC CTG CCG CTT CTG-3' (FRAG 977) (SEQ ID NO:10356)  
 5'-GCT GGG CCC CGG GCG CCC CCT-3' (FRAG 978) (SEQ ID NO:10357)  
 45 5'-CCC CTC TTG CTC GGG TCC CCG TG-3' (FRAG 979) (SEQ ID NO:10358)  
 5'-ACAGCGCGTCTGTCTCTCCAGCAGCATGGCCGGGCCAGCTGGGCCCC-3' (FRAG 980) (SEQ ID NO:10359)  
 5'-BCBGCGGCTCTGTGTCTCCBGCBGTGGCCGGCCBGCTGGGCCCC-3' (FRAG 981) (SEQ ID NO:10360)  
**Human Adenosine A3 Receptor Nucleic Acid and Antisense Oligonucleotide Fragments**  
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 GGGGACAACG TATTATTGAT ATTATTGTCT GTTTTCTCTC TTCCCAATAG AAGAATAAGT CATGGAGCCT GAAGGGTGGC  
 TAGTTGACTT ACTGACAAAA GGCTCTAGTT GGGCTGAACA TGTGTGTTG GGTGACTCAT TTCCATGCA TTGTGGAAT  
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 65 5'- CTGCTGAAT TTATTTTGA CTGTACATAT TTAGATGCTT AAGGTAAAAA TGATAAAGCC CTCAAGCCAC TGTGTGGGTT  
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 AACCAAGTGG GTCCCCAAAT AACTATGGCG TGCAAGTGTG TGGTCCAG AAGTTGGTGA CTAGGTAAGC GACTCAGGGA  
 GAGGGGCTGA TTCCAGACA GTCCGCTGTT CTGCTGGGA TGGGGCTGAG GCTTGGGAA TGTGGGCAGG AGGATATGCC  
 70 ATTGTACTT GTTGACAGC TTCTTTTCCC TCTTCTGTT ATGTCTGTT ATCTGTCTAT TCTGTGCTCT CTCACATAGG  
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 GCAGGTGTGA TGCTTCTCAG AGGTGCTGAG TTTTGGCCCT CTGAGCAGG GAATCTTTC TTATCCCTTT GACCAAGGAT  
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 75 CTAAGCTGGC AGAAAGATTG CATAATCAGT GCTTCCAGT CCGTCCAC CTGATCCTG ACTGTCTCT GGTCCCTGAA  
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TGCTGAGAGT TACTGAGCTC TGTACTTCCT CTGGGCCCAT CTCACTTCCT GAAACACCCC TGAAGAGGGT TGCTTATCTT  
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 5 GGAATTTTAG ACTGTCACTG CACATGGACC TCTGGGAAGA CGTCTGGCGA GAGCTAGGCC CACTGGCCCT ACAGACGGAT  
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 GACTTGGATC AACTTGGGAT ACAGGGTGGG GGTGCGGAGT GGAATCAATG AATGATGCCA GAGCAGATCA ACTAACAGA  
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 20 AAGCACCTGA ACCAAGTGGG TCCCAAATA ACAATGGCGT GCAAGTGTCT GGTTCACAGA AGTTGGTGAC TAGGTAAGCA  
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 AGCAAGTTGG GAATTTTAGA CTGTCACTGC ACATGGACCT CTGGGAAGAC GTCTGGCGAG AGCTAGGCCC ACTGGCCCTA  
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 35 CATTGGCCAA TGTACCTAC ATCACCATGG AAATTTTCTT TGGACTCTGC GCCATAGTGG GCAACGTGCT GCTCATCTGC  
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 (SEQ ID NO:11806)  
 5'-CGAATTCGGG GGACATCTGT TTGGGGAAGT AAGAGCAGCA GCACTTTCAG ATTCAGTCCA TATAGAGCTG TCCTACAGCA  
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 TTTCCAAGAG ATCACCACCC CAGAAAAAGG TAGGAATGAG CAAGTTGGGA ATTTTAGACT GTCACTGCAC ATGGACCTCT  
 40 GGAAGACGCT CTGGCGAGAG CTAGGCCAC TGGCCCTACA GACGGATCTT GCTGGCTCAC CTGTCCCTGT GGAGGTTCCC  
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 GACTCTGCGC CATAGTGGGC AACGTGCTGG TCATCTGCGT GGTCAGCTG AACCCACGCC TGCAGACCAC CACCTTCTAT  
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 50 GTACCAAGA AATGTCACCT TCCTTTCATG CCAATTTGTT TCCGCTATGA GGATGGACTA CATGGTATAC TTCAGCTTCC  
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 55 TGCTGTACAT GGGCATCTG CTGTCCCATG CCAACTCCAT GATGAACCCCT ATCGTCTATG CCTATAAAAT AAAGAAGTTC  
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 TTCTGAGTAG TTATCCATCA GAGATGACTC TGTCTCATTT ACCTTCAGAT TCCCCATCAA CAAACACTTG AGGGCTGTA  
 TGCTGGGCCC AAGGGATTTT TACATCCTTG ATTACTTCCA CTGAGGTGGG AGCATCTCCA GTGCTGCCCC ATTATATCTC  
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 60 GGGGACAACG TATTATTGAT ATTATTGTCT GTTTTCTCTT TTCCCAATAG AAGAATAAGT CATGGAGCCT GAAGGGTGGC  
 TAGTTGACTT ACTGACAAAA GGCTCTAGTT GGGCTGAACA TGTGTGTGGT GGTGACTCAT TTCCATGCCA TTGTGGAATT  
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 65 GACTGATTCC AAAAGAACTC ACCTATGTAC TGGGGTAGGG GAGGGAGGGT TTTTTCAGT ATTTAACTAA GGTTCAAAAGA  
 GTGCTATATA GTGAGAAAGG CTCTTTTTTT TTTTGGCA GAGTGCTGCC TCCTAGAAAT TTCTCTGGT  
 AACTTCCTTC TCTGAAGCAC AGATAAAGAA AACAATTACA GTAGAAACAT TTATGAGGGA CACATTGGAG GCCGATGAAG  
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 70 GGAATGCTCT TTTTAAATGTC TGGGGAGTCT GCTCAGGGAG AAATGACAAG TCTGGCGGGG ACAAGTATGG GATTGGTTAA  
 GACTTGGATC AACTTGGGAT ACAGGGTGGG GGTGCGGAGT GGAATCAATG AATGATGCCA GAGCAGATCA ACTAACAGA  
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 75 TGTGGGTTTG GTGCCAAGTG TTCTTCTTGT CTGCCTCTCT AACACGCCCT GTTAAAAATA TCCCTTTTGA TGGTCTGAG  
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- GAGGATATGC CATTTGATTC TGTTCACAC GTTCTTTTCC CTCTTTCTG TATGTCTGGT CATCTGCTA TTCTGCTGT  
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TGGAGGCTAA GCAGGTGTGA TGCTTCTCAG AGGTGCTGAG TTTTGTCCCT TCTGAGCAGG GAATCTTTGC TTATCCCTTT  
5 GACCAAGGAT CTTTGTGCA AAGGCTGGGT ATCGGCTGTG CTCAGCAAAG CGTCAACTCG TGCAAGAACT TAGCAGGAAT  
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TACTGCTTAT CTTTACCCAC CCTCCATCA TGTCTTGT GGCATCGCT GTGGACCGAT ACTTGGCGGT CAAGCTTACC  
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- 20 5'-GGGCAATTG TTAGTTATCC GCCGCCACCA AGACGCGGCA CGGCGCCTGG ACCGGAGGGG CCCCCTCGCG GCGCGAACTT  
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CGGGGGGCCC CGACCCGTGG GTCCCGGCCA CCAGCGCCCC AGCCCCGAGG CTCAGAAGCG GCAGGCGGAG GCGCGTCCG  
GGCGCTATGG CCATGCCCGG CGGGTCTCAC GCGGCTGCC CTGCGCCGCG GCGCTTCTCG TAGGGGGCGC CCGGGGCCA  
GCTGGCCCGG CCATGCTGTG GGAGACACAG GACGCGCTGT ACCTGGCGCT GGAGCTGGTC ATCGCCGCGC TTTCGTGGC  
25 GGGCAACGTG CTGGTGTGCG CCGCGGTGGG CACGGCGAAC ACTCTGCAGA CGCCACCAA CTACTTCTG GTGTCCCTGG  
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30 CCTGGGATG GAACACGAA TGAAAGCTGC TGCCTTGTA AGTGTCTCT TGAGAATGTG GTCCCATGA GCTACATGGT  
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35 ATGCTTACCG GAACCGAGAC TTCCGCTACA CTTTTCACAA AATTATCTCC AGGTATCTC TGTGCCAAGC AGATGTCAAG  
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40 TTTAAAGTC TGCCTGTTT ATGGTGGAAA ATACTGAAA CTATTTTACT GTGAAACAGT GTGAACATT ATAATGCAAA  
TTCTTTTAA CTAGAGGCA ATGAAAAAT AAAAGTTGAC TGTACTAAAA ATG-3' (FRAG. NO.: ) (SEQ ID NO:11794)
- 5'-GBG CB TGC-3' (FRAG. NO:1676) (SEQ ID NO:11060)  
5'-TTG TTG GGC-3' (FRAG. NO:1677) (SEQ ID NO:11061)  
5'-TGC CTT CCC BGG G-3' (FRAG. NO:1678) (SEQ ID NO:11062)
- 45 5'-GTT GTT GGG CAT CTT GCC-3' (FRAG. NO:1679) (SEQ ID NO:9372)  
5'-GTG GGC CTA GCT CTC GCC-3' (GRAG. NO:1680) (SEQ ID NO:9374)  
5'-ACA GAG CA TGC TGT TGT TGG GCA TCT TGC CTT CCC AGG G-3' (FRAG 982) (SEQ ID NO:10361)  
5'-BCB GBG CB TGC TGT TGT TGG GCB TCT TGC CTT CCC BGG G-3' (FRAG 983) (SEQ ID NO:10362)  
5'-CCC TTT TCT GGT GGG GTG-3' (FRAG 984) (SEQ ID NO:10363)
- 50 5'-GTG CTG TTG TTG GGC-3' (FRAG 985) (SEQ ID NO:10364)  
5'-TTT CTT CTG TTC CC-3' (FRAG 986) (SEQ ID NO:10365)  
5'-CCC TTT TCT GGT GGG GTG-3' (FRAG 987) (SEQ ID NO:10366)  
5'-GTG CTG TTG TTG GGC-3' (FRAG 988) (SEQ ID NO:10367)  
5'-TTT CTT CTG TTC CC-3' (FRAG 989) (SEQ ID NO:10368)
- 55 **Human IgE Receptor (Nucleic Acid and Antisense Oligonucleotide Fragments)**  
5'-TTT CCC CTG GGT CTT CC CTC CTG CTC TTT TTT C ATT TGC TCT CCT ATT ACT TTC TGT GTC CAT TTT TTC ATT AAC CGA  
GCT GT BTT TGC TCT CCT BTT BCT TTT TGT GTC CBT TTT TTC BTT BBC CGB GCT GT-3' (FRAG. NO:1681) (SEQ ID NO:1063)  
5'-CCG CTG GG-3' (FRAG. NO:1682) (SEQ ID NO:1064)  
5'-GCTCTCTBTT-3' (FRAG. NO:1683) (SEQ ID NO:1065)  
60 5'-CBTTBBCCBGCTG-3' (FRAG. NO:1684) (SEQ ID NO:1066)  
5'-TTT CCC CTG GGT CTT CC-3' (FRAG 990) (SEQ ID NO:10369)  
5'-CTC CTG CTC TTT TTT C-3' (FRAG 991) (SEQ ID NO:10370)  
ATTTGCTCTCTATTACTTTCTGTGTCATTTTTTCATTAAACCGAGCTGT (FRAG 992) (SEQ ID NO:10371)  
BTTTGTCTCTCTBTTBCTTTCTGTGTCCTTTTTCBTTBBCCBGCTGT (FRAG 993) (SEQ ID NO:10372)
- 65 **Human Fc-γ Receptor CD23 Antigen (IgE Receptor)**  
Nucleic Acid and Antisense Oligonucleotide Fragments  
5'-GCC TGT GTC TGT CCT GCT TCG TTC CTC TCG TTC CTG CTT GGT GCC CTT GCC G GTC CTG CTC CTC CGG GCT GTG G  
GTC GTG GCC CTG GCT CCG GCT GGT GGG CTC CCC TGG CCT TCG CTG GCT GGC GGC GTG C GGG TCT TGC TCT GGG CCT  
GGC TGT GGC CGT GGT TGG GGG TCT TC GCT GCC TCC GTT TGG GTG GC TCT CTG AAT ATT GAC CTT CCT CCA TGG CGG  
70 TCC TGC TTG GAT TCT CCC GA TCT CTG BBT BTT GBC CTT CCT CCB TGG CGG TCC TGC TTG GBT TCT CCC GB-3' (FRAG  
1685) (SEQ ID NO:11067)  
5'-GT CCT CCT-3' (FRAG 1686) (SEQ ID NO:11068)  
5'-TGT GTC TGT CCT CC-3' (FRAG 1687) (SEQ ID NO:11069)  
5'-GTG GCC CTG GC-3' (FRAG 1688) (SEQ ID NO:11070)

- 5'-CGT GGT TGG GG-3' (FRAG 1689) (SEQ ID NO:11071)  
 5'-TCT CTG BBT BTT GBC C-3' (FRAG1690) (SEQ ID NO:11072)  
 5'-GCC TGT GTC TGT CCT CCT-3' (FRAG 994) (SEQ ID NO:10373)  
 5'-GCT TCG TTC CTC TCG TTC-3' (FRAG 995) (SEQ ID NO:10374)  
 5'-CTG CTT GGT GCC CTT GCC G-3' (FRAG 996) (SEQ ID NO:10375)  
 5'-GTC CTG CTC CTC CGG GCT GTG G-3' (FRAG 997) (SEQ ID NO:10376)  
 5'-GTC GTG GCC CTG GCT CCG GCT GGT GGG CTC CCC TGG-3' (FRAG 998) (SEQ ID NO:10377)  
 5'-CCT TCG CTG GCT GGC GGC GTG C-3' (FRAG 999) (SEQ ID NO:10378)  
 5'-GGG TCT TGC TCT GGG CCT GGC TGT-3' (FRAG 1000) (SEQ ID NO:10379)  
 5'-GGC CGT GGT TGG GGG TCT TC-3' (FRAG 1001) (SEQ ID NO:10380)  
 5'-GCT GCC TCC GTT TGG GTG GC (FRAG 1002) (SEQ ID NO:10381)  
 5'-TCT CTG AAT ATT GAC CTT CCT CCA TGG CGG TCC TGC TTG GAT TCT CCC GA (FRAG 1003) (SEQ ID NO:10382)  
 5'-TCT CTG BBT BTT GBC CTT CCT CCB TGG CGG TCC TGC TTG GBT TCT CCC GB (FRAG 1004) (SEQ ID NO:10383)
- Human IgE Receptor (Subunit Nucleic Acid and Antisense Oligonucleotide Fragments)**
- 5'-GCC TTT CCT GGT TCT CTT GTT GTT TTT GGG GTT TGG CTT ACA GTA GAG TAG GGG ATT CCA TGG CAG GAG CCA TCT  
 TCT TCA TGG ACT CC TTC AAG GAG ACC TTA GGT TTC TGA GGG ACT GCT AAC ACG CCA TCT GGA GC BCB GTB GBG TBG  
 GGG BTT CCB TGG CBG GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTB GGT TTC TGB GGG BCT GCT BBC BCG  
 CCB TCT GGB GC GTT GTT TTT GGG GTT TGG CTT GCC TTT CCT GGT TCT CTT BCB GTB GBG TBG GGG BTT CCB TGG CBG  
 GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTB GGT TTC TGB GGG BCT GCT BBC BCG CCB TCT GGB GC-3'  
 (FRAG. NO: 1691) (SEQ ID NO:11073)  
 5'-TGG BCT CC -3' (FRAG. NO: 1692) (SEQ ID NO:11074)  
 5'-CCB TCT GGB-3' (FRAG. NO: 1693) (SEQ ID NO:11075)  
 5'-CT GCT BBC BCG-3' (FRAG. NO: 1694) (SEQ ID NO:11076)  
 5'-GTT TTT GGG GTT TG-3' (FRAG. NO: 1695) (SEQ ID NO:11077)  
 5'-GCC TTT CCT GGT TCT CTT GTT GTT TTT GGG GTT TGG CTT-3' (FRAG. NO:1005) (SEQ ID NO:10384)  
 5'-ACAGTAGAGTAGGGGATTCCATGGCAGGAGCCATCTTCTTCATGGACTCC-3'(FRAG.NO:1006)(SEQ ID NO:10385)  
 5'-TTC AAG GAG ACC TTA GGT TTC TGA GGG ACT GCT AAC ACG CCA TCT GGA GC-3' (FRAG. NO:1007) (SEQ ID NO:10386)  
 5'-BCB GTB GBG TBG GGG BTT CCB TGG CBG GBG CCB TCT TCT TCB TGG BCT CC TTC BBG GBG BCC TTB GGT TTC TGB  
 GGG-3' (FRAG. NO:1008) (SEQ ID NO:10387)  
 5'-BCT GCT BBC BCG CCB TCT GGB GC-3' (FRAG. NO:1009) (SEQ ID NO:10388)  
 5'-GTT GTT TTT GGG GTT TGG CTT-3' (FRAG. NO:1010) (SEQ ID NO:10389)  
 5'-GCC TTT CCT GGT TCT CTT-3' (FRAG. NO:1011) (SEQ ID NO:10390)  
 5'-BCBGTBGBGTBGGGGBTTCBTGGCBGGGCCBTCTTCTTCBTGGBTCC-3'(FRAG.NO:1012) (SEQ ID NO:10391)  
 5'-TTC BBG GBG BCC TTB GGT TTC TGB GGG BCT GCT BBC BCG CCB TCT GGB GC-3' (FRAG.NO:1013) (SEQ ID NO:10392)
- Human IgE Receptor (Fc Epsilon R) Nucleic Acid and Antisense Oligonucleotide Fragments**
- 5'-GCC TGT GTC TGT CCT CCT GCT TCG TTC CTC TCG TTC CTG CTT GGT GCC CTT GCC G GTC CTG CTC CTC CGG GCT GTG G  
 GTC CTC GCC CTG GCT CCG GCT GGT GGG CTC CCC TGG CCT TCG CTG GCT GGC GGC GTG C CCC BGB BCG BGB CCC GGB  
 CCG BCB GGC CGT GGT TGG GGG TCT TC GCT GCC TCC GTT TGG GTG GC GAT CTC TGA ATA TTGA CCT TCC ATG GCG GTC  
 CTG CTT GGA GBT CTC TGB BTB TTGB CCT TCC BTG GCG GTC CTG CTT GGB-3' (FRAG: 1696) (SEQ ID NO:11078)  
 5'-TCG TTC CTC TCG-3' (FRAG: 1697) (SEQ ID NO:12370)  
 5'-BGB BCG BGB C-3' (FRAG: 1698) (SEQ ID NO:11080)  
 5'-TGB BTB TTGB-3' (FRAG: 1699) (SEQ ID NO:11081)  
 5'-GCC TGT GTC TGT CCT CCT-3' (FRAG. NO:1014) (SEQ ID NO:10393)  
 5'-GCT TCG TTC CTC TCG TTC-3' (FRAG. NO:1015)(SEQ ID NO:10394)  
 5'-CTG CTT GGT GCC CTT GCC G-3' (FRAG. NO:1016)(SEQ ID NO:10395)  
 5'-GTC CTG CTC CTC CGG GCT GTG G-3' (FRAG. NO:1017)(SEQ ID NO:10396)  
 5'-GTC CTC GCC CTG GCT CCG GCT GGT GGG CTC CCC TGG-3' (FRAG. NO:1018) (SEQ ID NO:10397)  
 5'-CCT TCG CTG GCT GGC GGC GTG C-3' (FRAG. NO:1019) (SEQ ID NO:10398)  
 5'-CCC BGB BCG BGB CCC GGB CCG BCB-3' (FRAG. NO:1020) (SEQ ID NO:10399)  
 5'-GGC CGT GGT TGG GGG TCT TC-3' (FRAG. NO:1021) (SEQ ID NO:10400)  
 5'-GCT GCC TCC GTT TGG GTG GC-3' (FRAG. NO:1022) (SEQ ID NO:10401)  
 5'-GBT CTC TGB BTB TTGB CCT TCC BTG GCG GTC CTG CTT GGB-3' (FRAG. NO:1023) (SEQ ID NO:10402)
- Human High Affinity IgE Receptor Oligonucleotide Fragments**
- 5'-AACAAAGAAAA GCGTTGGTAG CTCTGGTGAA TCCCAAAAGA ATGTGGCAGT TGCTAGCCAT GCTCCTGAAT ATGTATAAAC  
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60 GCTCCAGATG GCGTGTAGC AGTCCCTCAG AAACCTAAGG TCTCTTGAA CCTCCATGG AATAGAATAT TTAAGGAGA  
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70 AATAGTAAGT GCTCAATTA CATTGGTTGA ATAAATGAGA GAATGAATAG ATTCAATTAT TAGCATTTGT AAAAGAGATG  
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CGTCTCTACT AAAAATACTA AAAATTAGCC GGGGNGTGGT GGTGGGTACA CCTGTAGTCC CAGCTACTTG GAGGCTGAGG  
CTGGAGAATC ACGTGAAC-3' (FRAG. NO: ) (SEQ ID NO:11873)

**Human Histidine Decarboxylase Nucleic Acid and Antisense Oligonucleotide Fragments**

- 5 5'-TCT CCC TTG GGC TCT GGC TCC TTC TC TCT CTC TCC CTC TCT CTC TGT CGC CTC CGC CCT GGC TGC TGG GGT GGT  
GGT GC TTT TGT TCT TCC TTG CTG CC GCC CCG CTG CTT GTC T TC CTC G CTC TGT CCC TCT CTC TCT GTB CTC CTC BGG  
CTC CBT CBT CTC CCT TGG GC-3' (FRAG. NO:1700) (SEQ ID NO:11082)  
5'-GGC TCT GGC (FRAG. NO:1701) (SEQ ID NO:11083)  
5'-CCC TTG G (FRAG. NO:1702) (SEQ ID NO:11084)  
5'-TT TGT TCT TCC (FRAG. NO:1703) (SEQ ID NO:11085)  
10 5'-TCT CCC TTG GGC TCT GGC TCC TTC TC-3' (FRAG. NO:1024) (SEQ ID NO:10403)  
5'-TCT CTC TCC CTC TCT CTC TGT -3' (FRAG. NO:1025) (SEQ ID NO:10404)  
5'-CGC CTC CGC CCT GGC TGC TGG GGT GGT GC-3' (FRAG. NO:1026) (SEQ ID NO:10405)  
5'-TTT TGT TCT TCC TTG CTG CC-3' (FRAG. NO:1027) (SEQ ID NO:10406)  
5'-GCC CCG CTG CTT GTC T TC CTC G-3' (FRAG. NO:1028) (SEQ ID NO:10407)  
15 5'-CTC TGT CCC TCT CTC TCT GTB CTC CTC BGG CTC CBT CBT CTC CCT TGG GC (FRAG. NO:1029) (SEQ ID NO:10408)

**Human Beta Tryptase Nucleic Acid and Antisense Oligonucleotide Fragments**

- 5'-CTT GCT CCT GGG GGC CTC CTG GTC CCT CCG GGT GTT CCC GGC GGG CCT GGC CTG GGG CBG GGG CCG CGT BGG CGC  
GGC TCG CCB GGB CGG GCB GCG CCB GCB GCB GCB GBT TCB GCB TCC TGG-3' (FRAG. NO:1704) (SEQ ID NO:11086)  
5'-GCT CCT GGG GGC CT-3' (FRAG. NO:1705) (SEQ ID NO:11087)  
20 5'-CGT BGG CGC-3' (FRAG. NO:1706) (SEQ ID NO:11088)  
5'-T GGC CTG GGG-3' (FRAG. NO:1707) (SEQ ID NO:11089)  
5'-CTT GCT CCT GGG GGC CTC CTG-3' (FRAG. NO:1030) (SEQ ID NO:10409)  
5'-GTC CCT CCG GGT GTT CCC GGC-3' (FRAG. NO:1031) (SEQ ID NO:10410)  
5'-GGG CCT GGC CTG GGG CBG GGG CCG CGT BGG CGC GGC TCG CCB GGB CGG GCB GCG CCB GCB GCB GBT TCB GCB  
25 TCC TGG-3' (FRAG. NO:1032) (SEQ ID NO:10411)

**Human Tryptase-I Nucleic Acid and Antisense Oligonucleotide Fragments**

- 5'-CTT GCT CCT GGG GGC CTC CTG GTC CCT CTG GCT G TT CCC GGC CCT GGB CTG GGG CBG GGG CCG CGT BGG CGC GGC  
TCG CCB GGB CGG GCB GCG CCB GCB GCB GCB GGC TCB GCB TCC TGG CCB CGG BBT TCC-3' (FRAG. NO: 1708) (SEQ ID  
NO:11090)  
30 5'-CT CCT GGG GGC CTC CTG-3' (FRAG. NO:1709) (SEQ ID NO:11091)  
5'-B TCC TGG CCB CGG BBT TCC -3' (FRAG. NO:1710) (SEQ ID NO:11092)  
5'-GTC CCT C-3' (FRAG. NO:1711) (SEQ ID NO:11093)  
5'-CTT GCT CCT GGG GGC CTC CTG-3' (FRAG. NO:1033) (SEQ ID NO:10412)  
5'-GTC CCT CTG GCT G TT CCC GGC-3' (FRAG. NO:1034) (SEQ ID NO:10413)  
35 5'-CCT GGB CTG GGG CBG GGG CCG CGT BGG CGC GGC TCG CCB GGB CGG GCB GCG CCB GCB GCB GCB GGC TCB GCB TCC  
TGG CCB CGG BBT TCC -3' (FRAG. NO:1035) (SEQ ID NO:10414)

**Human Prostaglandin D Synthase Nucleic Acid and Antisense Oligonucleotide Fragments**

- 5'-GGT GTG CGG GGC CTG GTG CC CCT GGG CCT CGG GTG CTG CCT GT GCG CTG CCT TCT TCT CCT GG GTC CTC GCC GGG  
GCC CTT GCT GCC CTG GCT GT GCC CTG GGG GTC TGG GTT CGG CTG T CCC CBG CBG GBC CBG TCC CBT CCB CBG CGT  
40 GTG BTG BGT BGC CBT TCT CCT GCB GCC GGB-3' (FRAG. NO:1712) (SEQ ID NO:11094)  
5'-T TCT CCT GCB GCC GGB -3' (FRAG. NO:1713) (SEQ ID NO:11095)  
5'-CTT GCT GCC CTG GCT GT-3' (FRAG. NO:1714) (SEQ ID NO:11096)  
5'-TCT TCT CCT GG-3' (FRAG. NO:1715) (SEQ ID NO:11097)  
5'-GGT GTG CGG GGC CTG GTG CC-3' (FRAG. NO:1036) (SEQ ID NO:10415)  
45 5'-CCT GGG CCT CGG GTG CTG CCT GT-3' (FRAG. NO:1037) (SEQ ID NO:10416)  
5'-GCG CTG CCT TCT TCT CCT GG-3' (FRAG. NO:1038) (SEQ ID NO:10417)  
5'-GTC CTC GCC GGG GCC CTT GCT GCC CTG GCT GT-3' (FRAG. NO:1039) (SEQ ID NO:10418)  
5'-GCC CTG GGG GTC TGG GTT CGG CTG T-3' (FRAG. NO:1040) (SEQ ID NO:10419)  
5'-CCC CBG CBG GBC CBG TCC CBT CCB CGT GTG BTG BGT BGC CBT TCT CCT GCB GCC GGB -3'  
50 (FRAG. NO:1041) (SEQ ID NO:10420)

**Human Cyclooxygenase-2 Nucleic Acid and Antisense Oligonucleotide Fragments**

- 5'-GGG CGC GGG GCB GCB TCG C TTT GGG CTT TTC TCC TTT GGT T TGB GCG CCB GGB CCG CGC BCB GCB GCB GGG CGC  
GGG CGB GCB TCG CBG CGG CGG GCB GGG-3' (FRAG. NO: 1716) (SEQ ID NO:11098)  
5'-G GCB GGG -3' (FRAG. NO: 1717) (SEQ ID NO:11099)  
55 5'-TCC TTT GGT T-3' (FRAG. NO:1718) (SEQ ID NO:11100)  
5'-GGG CGC GGG GCB GCB TCG C-3' (FRAG. NO:1042) (SEQ ID NO:10421)  
5'-TTT GGG CTT TTC TCC TTT GGT T-3' (FRAG. NO:1043) (SEQ ID NO:10422)  
5'-TGB GCG CCB GGB CCG CGC BCB GCB GCB GGG CGC GGG GCB GCB TCG CBG CGG CGG GCB GGG -3'  
(FRAG. NO:1044) (SEQ ID NO:10423)

**Human Eosinophil Cationic Protein Nucleic Acid and Antisense Oligonucleotide Fragments**

- 5'-CCT CCT TCC TGG TCT GTC TGC CBG BCB BBT TTG GGB BGT GBB CBG TTT TGG BBC CBT GTT TCC CBG TCT CTG BGC  
TGT GGC-3' (FRAG. NO: 1719) (SEQ ID NO:11101)  
5'-TTC TCC TTT GGT T-3' (FRAG. NO:1720) (SEQ ID NO:11102)  
5'-T TTC TCC TTT GGT T-3' (FRAG. NO:1721) (SEQ ID NO:11103)  
65 5'-GGG CGC GGG GCB GCB TCG C-3' (FRAG. NO:1042) (SEQ ID NO:10421)  
5'-TTT GGG CTT TTC TCC TTT GGT T-3' (FRAG. NO:1043) (SEQ ID NO:10422)  
5'-TGB GCG CCB GGB CCG CGC BCB GCB GCB GGG CGC GGG GCB GCB TCG CBG CGG CGG GCB GGG -3'  
(FRAG. NO:1044) (SEQ ID NO:10423)

**Human Eosinophil Derived Neurotoxin Nucleic Acid and Antisense Oligonucleotide Fragments**

- 70 5'-GCC CTG CTG CTC TTT CTG CT TCC CTT GGT GGG TTG GGC C GCT GGT TGT TCT GGG GTT C TTG CTG CCC CTT CTG TCC C  
TGT TTG CTG GTG TCT GCG C 5'-CCC CBB CBG BBG BBG CBG BCB BBT TTG GGB BGT GBB CBG TTT TGG BBC CBT GTT TCC  
TGT-3' (FRAG. NO: 1722) (SEQ ID NO:11104)  
5'-TTC CTG T-3' (FRAG. NO:1723) (SEQ ID NO:11105)

5'-CTC TTT CTG CT-3' (FRAG. NO: 1724) (SEQ ID NO:11106)  
 5'-CCC CTT CTG TCC C-3' (FRAG. NO:1725) (SEQ ID NO:11107)  
 5'-GCC CTG CTG CTC TTT CTG CT-3' (FRAG. NO:1047) (SEQ ID NO:10424)  
 5'-TCC CTT GGT GGG TTG GGC C-3' (FRAG. NO:1048) (SEQ ID NO:10425)  
 5'-GCT GGT TGT TCT GGG GTT C-3' (FRAG. NO:1049) (SEQ ID NO:10427)  
 5'-TTG CTG CCC CTT CTG TCC C-3' (FRAG. NO:1050) (SEQ ID NO:10426)  
 5'-TGT TTG CTG GTG TCT GCG C-3' (FRAG. NO:1051) (SEQ ID NO:10428)  
 5'-CCC CBB CBG BBG CBG BCB BBT TTG GGB BGT GBB CBG TTT TGG BBC CBT GTT TCC TGT-3' (FRAG. NO:1052) (SEQ ID NO:10429)

# **Human Eosinophil Peroxidase Nucleic Acid and Antisense Oligonucleotide Fragments**

5'-GCG CTC GGC CTG GTC CCG G GGG TCT CCT CTT GTT GTT GC TTG CGC CTC CTG CTG GGG GT CC CTC TGT TCT TGT TTT  
 GGG GGC GGG CCC GGC CGT TGT CTT G GTT TGG GGG TTT CCG TTG GGG TTC TCC TGG CCC GGG CCT TGC CC GGC CGT  
 GGT CCC GGC TTC GTTCTT GTC TCC GTC TCG GCT CTT CTG GGG CCT TGC GCT GTC TTT GGT G 5'-GCB CCG TCC BGT GBT  
 TGT GCG GTB CTT GTC GCT GCB GCG CTC GGC CTG GTC CCG GBG BGC CACCGCTCCT GTCAGCCAAC AAATATCCAT  
 15 TGAGCGACAC CTGTGTCCCA GGTGCTGCTC TGGGCCCTGG GAGAAGTGCA TCAGTGGGCT TGGTAGTAGA GGGTAGGGAT  
 GGAGTGAAGG GTAGGCAGGA AGAATGTCCC CAGGCTGGTA GGAGGTGGGG TGGGGGGTTT CAGTCTCAAA ACTCCCATGA  
 AAACAGAGAGA GAAGTTTCAG AACTCCACCC AAGAGGCTGG GTTCTAGGG CCCAGAGCTG CCCTCCCCCA CCTAGAAATG  
 GGCTATAAAA GTCCCTTCCC AGCTACGTCC AGAGAAGAGC TGGAGGAAGT GAGAGGTCCG CTGGGGGTCC TCAAAAGTGAG  
 AGGGGAGCAG AGGATCCTCC CGTGCAGGCT GTGGATGTCA CTCACTTCCC AGCTGGTGAA GCCTCGCTGC AGAGATGCAT  
 20 CTGCTCCAG CCCTGGCAGG GGTCTGGCC ACATCTGTC TCGGCCAGCC CTGTGAGGGC ACTGACCCAG GTAATAGTCC  
 CCTAGACAGG CAAGGAGGAG GGAGGGGAAA TGGAAGGGGA AGCACTTGGG TCTTGGAGGG GGTCTTGTGG CTGTCTGAAC  
 CCTGAGTCCC CATCTCTTTG AACAGCTCC CTGGGGCAG TGGAGACCTC GGTCTGCGA GACTGCATAG CAGAGGCCAA  
 GTTGCTGTGT GATGCTGCCT ACAATTGGAC CCAGAAGAGG TGGACTTGGG TCTGGGGGCT GCATGGGCCT GGGAGGATCA GT  
 TAATACCTTG TGGGGTCAGG GAGCCCATGT CCGGTGCTGA TGTATTTC CCACCAAGTC CGGGCTGTCT CCAACAGAT  
 25 TGTGCGCTTC CCCAATGAGA GACTGACCTC CGACCGTGGC CGAGCCCTCA TGTTCATGCA GTGGGGCCAG TTCAATTGACC  
 ATGACCTGGA CTTCTCCCG GAGTCCCGG CCAGAGTGGC CTTCACTGCA GGCCTGACT GTGAGAGGAC CTGCGCCAG  
 CTGCCCCCT GCTTTCCAT CAAGGTACCT ACCCTCAGCC AATCTCCAT GCCCTTGTGT GGCCTCCCC AAAGGCAAGG  
 TGCTGGGGT GGGGATCTGG AAGACTGGAG CACCATCTT AGAGGAGCTG CTGTGGAGCT AGGGTATGAG ACAGAGACAC  
 AAG CACTGTCTCC TCTTCCATCT CAGATCCAC CCAATGACCC CGCATCAAG AACCAAGCTG ACTGCATCCC TTTCTCCGC  
 30 TCGGCACCTT CATGCCCA AAACAAGAAG AGAGTCCGCA ACCAGATCAA CGCGCTACC TCCTTTGTGG ACGCCAGCAT  
 TGTGTATGGC AGTGAGGTCT CCCTCTCGCT GCGGCTCCG AACCCGACCA ACTACCTGGG GCTGTGGCC ATCAACAGC  
 GCTTTCAAGA CAACGGCCGG GCCCTGCTGC CTTTCGACAA CTTGCACGAT GACCCCTGTC TCCTACCAA CCGCTCGGG  
 CGCATCCCTT GCTTCTGGC AGGTGAGACA GGGAGGAAGG TGGTGTCTC CCAGGAAACA GCCATCCCTG GGGTCCCAAC  
 TGGGAAGCAA TGGTGGGATG TGGTGAAGT ACATGTTTG GACCTCAGT ATTAGGCACA CCATAAGCAT GGAATCTGTG AC  
 35 TGAAGAGATG GAGGTCCAGT GAGGGCCAGG AGTTTGGCCC ACCCGTCTC TCCCATCCCC AGCCCTGGGT CTACCCTGGT  
 AGAAAGACAT TTCTCTGGGA AAGGCTCGAG TAAATCTGAG CTTGGGGTTT TCAAGGTGAC ACCCGATCAA CGGAAACCCC  
 CAAACTGGCA GCCATGACA CCTCTTTAT GCGAGAGCAC AACCGGCTGG CCACCGAGCT GAGACGCTG AATCCCCGT  
 GGAATGGAGA CAAACTGTAC AATGAGCTC GGAAGATCAT GGGGGCCATG TTCAGGTAA GGAGCTCTGC ATCCAGCAT  
 CCCC CTTTGTATCT CCACCCACCA ATAGTAAATT AATGTTGTCA CATTGACGT GATGACAATA AAGAATATGT  
 40 CTGAGCCACC CTTTGAAGG GCAAGGGTAT GGGTGAAGT CCTCTGGGA ATGTTCTCTC TGTCTTCCCT TCCAGATCAT  
 CACCTACCGA GACTTCTGTC CCTGTGTTCT GGGCAAGGCC CGGGCCAGGA GAACCCCTGGG GCATACAGG GGGTACTGCT  
 CCAATGTGGA CCCACGGGTG GCCAATGTCT TCACTCTGGC CTTCCGCTT GGCCACACAA TGCTCCAGCC CTTTATGTT  
 CGCTTGGACA GTGAGTACCG GGCTCCGCA CCAACTCGC ATGTCCACT TAGTCTGCTC TTTCTTGCCA GCTGGCGGAT  
 45 CGTGTATGAA GGTGACCAGG TTTTCCAGGG GGCAAAATGG GGTGAGGGTG GGGAGCATGC CTCTCCCTAG GTGG  
 TCCAGCTGCT TCATGTCTCT CCAGAACTCT GTTTCCTGAC AAACGTTACT AACATACCCG ACTGGCTTGT CCAGCTCTGG  
 GCTAGCTTGG CATCATGTGA TAACCCAAGT AGCTTCCAG AGGCTGGTCC AATCTGTGCT GCTCACATTC TGTGCCACCA  
 GGGGGCATCG AACCCATCTT CCGGGGCTC ATGGCCACCT GTCCAAAGCT GAACCGTCAG GATGCCATGT CAGTGAATGA  
 GCTCGGGAC CGGCTGTTTC GGCAAGTGAG GAGGATTGGG CTGGACCTGG CAGCTCTCAA CATGCAACGA AGCCGGGACC  
 50 ACGGCTTCC AGGTGAGGGG GCTGTCCACC TCTTCTCCCA GCTTGTCTCG GGCCAGGCTG CTCAAGGGGT TCTGGGAAGA  
 CCCTGGTACC GCACTGCTG GTAGGTTCTG GTGGCAGAAA CGAGGTGTTT TCACCAAAAG ACAGCGCAAG GCCCTGAGCA  
 GAAITTCCTT GTCTCGAATT ATATGTGACA ATACCGGTAT CACCACGGTT TCAAGGGACA TCTTCAGAGC CAACATCTAC  
 CCTCGGGCT TGTGAACTG CAGCCGTATC CCCAGGTGA ACCTATCAGC CTGGCGAGGG ACATGAGGCT TCTGCAGGTA  
 AGGGGAGGCC ACCTCCAGCA CCCTGGGCTG GTTAAGCCTC ACATCCTTCC CTGGATGGAT GGCTGAGTCC TCTTAGGTCT  
 55 CTAAGCAGAG AAGAACAGAA TTGTCACTAG GTACTCTTTC CAAGTGGCTT CCAATGTGTC TAGTTCCTG GCTGACAGTC  
 AATTCCAGGC CTAGGACTT TGGGGGAAA TTAGGAGCAT CCAACTA GAATTCCGTG GCCAGGACCC CTGCCAGGGC  
 ACTGACCCAG CCTCCCTGG GGCAGTGGAG ACCTCGGTCC TGCGAGACTG CATAGCAGAG GCCAAGTTC TGGTGGATGC  
 TGCCTACAAT TGGACCCAGA AGAGCATCAA GCAGCGGTT CGCAGCGGTT CAGCCAGCCC CATGGACCTC CTGTCTACT  
 TCAAACAACC GGTAGCAGCC ACCAGGACAG TTGTTCGGGC CGCAGATTAT ATGCATGTG CTTTGGGGCT GCTTGAAGAG  
 AAGTTACAAC CCCAGCGGTG CGGACCTTC ATTGTCACTG ATGTGTAAC AGAACACAG CTGCGGCTGC TGTCACAGG  
 60 CAGTGGCTGT GCTCTCCGG ACCAGGCCGA GCGCTGCAGC GACAAGTACC GCACCATCAC TGGACGGTGC AACAACAAGA  
 GGAGACCTT GCTAGGGGCC TCAACCCAGG CTCTGGCTCG CTGGCTGCC GCGAGTATG AGGATGGGCT GTCGCTCCCC  
 TTCGGCTGGA CCCCCAGCAG GAGGCGCAAT GGCTTCTTTC TCCCTCTGT CCGGGCTGTC TCAACCCAGA TTGTGCGCTT  
 CCCCAGTAC AGACTGACCT CCGACCGTGG CCGAGCCCTC ATGTTCATGC AGTGGGGCCA GTTCATTGAC CATGACCTGG  
 65 ACTTCTCCCC GGAGTCCCCG GCCAGAGTGG CTTTCACTGC AGGCGTTGAC TGTGAGAGGA CCTGCGCCCA GCTGCCCCC  
 TGCTTTCCCA TCAAGATCCC ACCCAATGAC CCCCAGATCA AGAACCCAGC TGAATGATC CTTTCTTCC GCTCGGCACC  
 GCATGAGGTT CTTCTCTCG CTGCGGCTCC GCAACCGGAC CAACTACCTG GGGCTGTGTT CCATCAACCA CGCTTTTCAA  
 GACAACGGCC GGGCCTGTCT GCCCTTCGAC AACCTGCAGC ATGACCCCTG TCTCCTCACC AACCGCTCG CGCGCATCCC  
 70 CTGCTTCTG CGAGGTGACA CCCGATCAAC GGAACCCCCC AAAGTGGCAG CCATGCACAC CCTTTTATG CGAGAGCACA  
 ACCGGCTGGC CACCGAGCTG AGACGCGTGA ATCCCGGTG GAATGGAGAC AAAGTGTACA ATGAGGCTCG GAAAGATCATG  
 GGGGCCATGG TCCAGATCAT CACCTACCGA GACTTCTGTC CCTGTGTTCT GGGCAAGGCC CCGGCCAGGA GAACCCCTGG  
 GCACTACAGG GGTACTGTCT CCAATGTGGA CCCACGGGTG GCCAATGTCT TCACCCTGGC CTTCCGCTTT GGGCACACAA  
 75 TGCTCCAGCC CTTTCTGACA GTCAGTACCG GCTTCCGCA CCAACTCGC ATGTCCACT ATGTCCACT ATGTCCACT ATGTCCACT  
 TTTCTTGCCA GCTGGCGGAT CGTGTATGAA GGGGGCATCG ACCCATCTC CCGGGGCTC ATGGCCACCC CTGCCAAGCT  
 GAACCGTCAG GATGCCATGT TAGTGGATGA GCTCCGGGAC CGGCTGTTTC GGCAAGTGAG GAGGATTGGG CTGGACCTGG



CAGCTCTCAA CATGCAACGA AGCCGGGACC ACGGCCTTCC AGGGTACAAT GCTTGGAGGC GCTTCTGTGG GCTCTCCAG  
 CCCCAGGAATT TGGCAGAGCT TAGCCGGGTG CTGAAAAACC AGGACTTGGC AAGGAAGTTC CTGAATTTGT ATGGAACACC  
 TGACAACATT GACATCTGGA TTGGGGCCAT CGCTGAGCGT CTTTGTCCGG GGGCTCGAGT GGGGCCTCTT CTGGCTTGTC  
 5 TGTTTCGAGAA CCAGTTCAGA AGAGCCGAGA CGGAGACAGG TTCTGGTGGC AGAACGAGGT GTTTTCACCA AAGACAGCGC  
 AAGGCCCTGA GCAGAAATTC CTTGTCTCGA ATTATATGTG ACAATACCGG TATCACCACG GTTTCAGAGG ACATCTTCAG  
 AGCCAACATC TACCTCGGG GCTTTGTGAA CTGCAGCCGT ATCCCCAGGT TGAACCTATC AGCCTGGCGA GGGACATGAG  
 GCTTCTGCAG GAGTCTATCC CAAGTCTCCA ACTTTTGGAG ACAAGGGGAA GGGGAGGACC ATGAGGCTGC CTGTCTTCCC  
 TGGAGCAAGT GCAGGCTCGT GACGCTTCTG CTGGCTACAG CTCAGAGCTG GTTCCCCAG CCAGGAGTGA AGGCTGGGGG  
 10 CTCCTATCAG CAATGGACCT TCCGCTTGG GAGCCTCTTA GGTATTAGGC TATGAATCAG CGCCACGTGC AAAGGCTTGG  
 GAGCCAAGCC ATGTGCTCTT GCACCCAGG CAAGAAAAGT CAGCTGGAGG GTTTACAGCA CTTTCTACTG TTTCCAGGCC  
 CTCCCTCCCC TCCCTACCA TGAATAAGAG ATCACTCGGT CCTAGCCTCC AGACACCCCA CAATACTCTC CTGAGCCTGA  
 GGCCAGGCAG CATGCTCTGC TTCTACCAAT AAGCACTGC CGGAATTC-3' (FRAG. NO: 1726) (SEQ ID NO:12377)  
 5'-CACCGCTCCT GTACGCCAAC AAATATCCAT TGAGCGACAC TGTGTCTCCA GGTGCTGCTC TGGGCCCTGG GAGAAGTGCA  
 TCAAGTGGCT TGGTAGTAGA GGGTAGGAT GGAGTGAAG GTAGCGAGGA AGAATGTCCC CAGGCTGGTA GGAGGTGGGG  
 15 TGGGGGGTTT GACTCTCAA ACTCCCATGA AAACCCAGAGA GAAAGTTTCAG AACTCCACCC AAGAGGCTGG GTTCTAGGG  
 CCCAGAGCTG CCCTCCCCCA CCTAGAAATG GGCTATAAAA GTCCCTTCCC AGCTACGTCC AGAGAAGAGC TGGAGGAAGT  
 GAGAGGTGCG CTGGGGGTCC TCAAAGTGAG AGGGAGCAG AGGATCTTCC CGTGCAGGCT GTGGATGICA CTCACTTCCC  
 AGCTGGCTGA GCCTCGCTGC AGAGATGCAT CTGCTCCAG CTGCTGGCAG GGTCTGGGCC AACTCTGCTC TCGCCAGGCC  
 CTGTGAGGGC ACTGACCCAG GTAATAGTCC CCTAGACAGG CAAGGAGGAG GGAGGGGAAA TGGAAAGGGGA AGCACTTGGG  
 20 TCTTGGAGGG GGTCTTGTGG CTGTCTGAAC CCTGAGTCCC CATCTCTTTG AACAGCCTCC CCTGGGGCAG TGGAGACCTC  
 GGTCTGCGA GACTGCATAG CAGAGGCCAA GTTGTGCTGGT GATGCTGCCT ACAATTGGAC CCAGAAAGAGG TGGACTTGGG  
 TCTGGGGGCT GCATGGGCCT GGGAGGATCA GT-3' (FRAG. NO: ) (SEQ ID NO:11852)  
 5'-TAATACCTTG TGGGGTCAGG GAGCCCATGT CCCGTGCTGA TGTATTTC CCACCAGGTC CGGGCTGTCT CCAACCAGAT  
 TGTGCGCTTC CCCAATGAGA GACTGACCTC CGACCGTGGC CGAGCCCTCA TGTTCATGCA GTGGGGCCAG TTCATTGACC  
 25 ATGACCTGGA CTTCTCCCG GAGTCCCGG CCAGAGTGGC CTTCACTGCA GCGGTGACT GTGAGAGGAC CTGCGCCAG  
 CTGCCCCCT GCTTTCCTC CAAGGTACCT ACCCTCAGCC AATCTCCAT GCCCTTGTGT GGCCTCCCC AAAGGCAAGG  
 TGCTGGGGT GGGGATCTGG AAGACTGGAG CACCATCCTT AAGGAGCTGC CTGTGAGCT AGGGTATGAG ACAGAGACAC  
 AAG-3' (FRAG.NO: ) (SEQ ID NO:11853)  
 5'-CACTGTCTCC TCTTCCATCT CAGATCCAC CCAATGACCC CCGCATCAAG AACCAGCGTG ACTGCATCCC TTCTTCCGC  
 30 TCGGCACCTC ATGCCCCCA AAACAAGAAC AGAGTCCGA ACCAGATCAA CGCGTCACC TCCTTTGTGG ACGCCAGCAT  
 GGTGTATGGC AGTGAGGTCT CCCTCTCGCT GCGGCTCCG AACCAGGACCA ACTACCTGGG GCTGCTGGCC ATCAACAGC  
 GCTTTCAGAA CAACGGCCCG GCGCTGCTGC CCTTCGACAA CCTGCACGAT GACCCCTGTC TCCTACCAA CCGCTCGGCG  
 CGCATCCCC TGTTCCTGGC AGGTGAGACA GGGAGGAAAG TGGTGTCTTC CCAGGAAACA GCCATCCCTG GGGTCCCAAC  
 TGGGAAGCAA TGTTGGGATG TGGTGAAGGT ACATGGTTTG GGACCTCAGT ATTAGGACCA CCATAAGCAT GGATCTGTGC AC-3'  
 35 (FRAG.NO: ) (SEQ ID NO:11854)  
 5'-TGAAGAGATG GAGGTCCAGT GAGGGCCAGG AGTTTGGGCC ACCCGTCTC TCCCATCCCC AGCCCTGGGT CTACCCTGGT  
 AGAAAGACAT TTCTTGGGA AAGGCTGCAG TAAATCTGAG CTTGGGGTTT TCAAGGTGAC ACCCGATCAA CGGAAACCCC  
 CAAACTGGCA GCCATGCACA CCCTCTTAT GCGAGAGCAC AACCAGCTGG CCACCGAGCT GAGACGCTG AATCCCCGGT  
 GGAATGGAGA CAAACTGTAC AATGAGGCTC GGAAGATCAT GGGGGCCATG GTCCAGGTAA GGAGCTCTGC ATCCAGCAT  
 40 CCCCC-3' (FRAG.NO: ) (SEQ ID NO:11855)  
 5'-CTTTGTATCT CCACCCACCA ATAGTAAATT AATGTTGTC CATTGACGT GATGACAATA AAGAATATGT CTGAGCCACC  
 CTTTGAAGAA GCAAGGGTAT GGGTGAGTAG CCTCTGGGGA ATGTTCTTCC TGTCTTCCCT TCCAGATCAT CACCTACCGA  
 GACTTCTGCG CCCTGTTCT GGGCAAGGCC CGGGCCAGG GAACCCCTGG GCACTACAGG GGGTACTGCT CCAATGTGGA  
 45 CCCACGGGTG GCCAATGTCT TCACCTGGC CTTCCGCTTT GGCCACACAA TGCTCCAGCC CTTTCATGTC CGCTTGGACA  
 GTCAGTACCG GGCCTCCGCA CCCAACTCGC ATGTCCCACT TAGCTCTGCC TTCTTTGCCA GCTGGCGGAT CGTGTATGAA  
 GGTGACCAGG TTTTCCAGG GGCAAATGGG GGTGAGGGTG GGGAGCATGC CCTCCCCTAG GTGG-3' (FRAG.NO: ) (SEQ ID  
 NO:11856)  
 5'-TCCAGCTGCT TCATGTCTCT CCAGAATCT GTTTCCTGAC AAACGTTACT AACATACCCG ACTGGCTTGT CCAGCTCTGG  
 GCTAGCTTGG CATCATGTGA TAACCCAAGT AGCTTCCAG AGGCTGGTCT AATCTGTGCT GCTCACATTC CTTGCCACCA  
 50 GGGGGCATCG ACCCATCTC CCGGGCCCTC ATGGCCACCC CTGCCAAGCT GAACCGTCAG GATGCCATGT TAGTGAGTGA  
 GCTCCGGGAC CGGCTGTTTC GGCAAGTGAG GAGGATTGGG CTGGACCTGG CAGCTCTCAA CATGCAACGA AGCCGGGACC  
 ACGGCCTTCC AGGTGAGGGG GCTGTCCACC TCTTCTCCCA GCTTGTCTCG GGCCAGGCTG CTCAAGGGGT TCTGGGAAGA  
 CCTGGTACC-3' (FRAG.NO: ) (SEQ ID NO:11857)  
 5'-CGACTGCCTG GTAGGTTCTG GTGGCAGAAA CGAGGTGTTT TCACCAAAAAG ACAGCGCAAG GCCCTGAGCA GAATTTCTTT  
 GTCTCGAATT ATATGTGACA ATACCGGTAT CACCACGGTT TCAAGGGACA TCTTCAGAGC CAACATCTAC CCTCGGGGCT  
 55 TTGTGAATCG CAGCCGTATC CCCAGGTTGA ACCTATCAGG CTGGCGAGGG ACATGAGGCT TCTGCAGGTA AGGGGAGGCC  
 ACCTCCAGCA CCCTGGGCTG GTTAAGCCTC ACATCCTTCC CTGGATGGAT GGCTGAGTCC TCTTAGGTCT CTAAGCAGAG  
 AAAACAGAAC TTGTCACTAG GTACTCTTTC CAAGTGGCTT CCAATGTGC TAGTTTCTGG GCTGACAGTC AATCCAGGC  
 CTTAGGACTT TGGGGGAAA TTAGGAGCAT CCAACTA-3' (FRAG.NO: ) (SEQ ID NO:11858)  
 60 5'-GAATTCCTG GCCAGGACCC CTGCCAGGC ACTGACCCAG CCTCCCTGG GGCAGTGGAG ACCTCGGTCC TGCGAGACTG  
 CATAGCAGAG GCCAAGTTGC TGGTGGATGC TGCTTACAAT TGGACCCAGA AGAGCATCAA GCAGCGGCTT CGCAGCGGTT  
 CAGCCAGCCC CATGGACCTC CTGTCTACT TCAAACAACC GGTAGCAGCC ACCAGGACAG TTGTTGGGG CGCAGATTAT  
 ATGCATGTGG CTTTGGGGCT GCTTGAAGAG AAGTTACAAC CCCAGCGGTC CGGACCCCTC ATTGTCACTG ATGTGCTAAC  
 65 AGAACCACAG CTGCGGCTGC TGTCCAGGC CAGTGGCTGT GCTCTCCGG ACCAGGCCGA GCGCTGCAG GACAAGTACC  
 GCACCATCAT TGGACGGTGC AACAACAAGA GGAGACCTTT GCTAGGGGCC TCCAACCAGG CTCTGGCTCG CTGGCTGCC  
 CGCAGTATG AAGATGGGCT GTCGCTCCC TTCCGGCTGA CCCCCAGCAG GAGGCGCAAT GGCTTCTTTC TCCTCTTGT  
 CCGGGCTGTC TCCAACCAGA TTGTGCGCTT CCCCATTGAG AGACTGACCT CCGACCGTGG CCGAGCCCTC ATGTTTATGC  
 AGTGGGGGCA GTTCAATTGAC CATGACCTGG ACTTCTCCC GAGTCCCGG GCCAGAGTGG CCTTCACTGC AGGCGTTGAC  
 TGTGAGAGGA CTTGCGCCCA GCTGCCCCC TGTCTTCCCA TGAAGATCCC ACCCAATGAC CCCCAGTAC AGAACCAGCG  
 70 TGAATGCATC CTTTCTTCC GCTCGGCACC CTCATGCCCC CAAAACAAGA ACAGAGTCCG CAACAGATC AACGCGCTCA  
 CCTCTTTGT GGACGCCAG ATGGTGTATG GCAATGAGGT CTCCCTCTCG CTGCGGCTCC GCAACCGGAC CAACTACCTG  
 GGCTGCTGG CCATCAACCA CGCTTTCAA GACAACGGCC GGGCCTGCT GCCCTTCGAC AACCTGCACG ATGACCCCTG  
 TCTCTCACC AACCGCTCG CGGCATCCC CTGCTTCTG GCAAGTGACA CCGGATCAAC GGAAACCCCC AAAGTGGCAG  
 75 CCATGCACAC CCTTTTATG CGAGAGCACA ACCGGCTGG CACCGAGCTG AGACGCTGA ATCCCCGGT GAATGGAGAC  
 AAAGTGTACA ATGAGGCTCG GAAGATCATG GGGGCCATGG TCCAGATCAT CACTACCGA GACTTCTGCG CCTGTTCTC

GGGCAAGGCC CGGGCCAGGA GAACCTGGG GCACTACAGG GGGTACTGCT CCAATGTGGA CCCACGGGTG GCCAATGTCT  
 TCACCTCGGC CTTCCTGTTT GGCCACACAA TGCTCCAGCC CTTCATGTTC CGTTGGGACA GTCAGTACCG GGCCTCCGCA  
 CCCAACTCGC ATGTCCCACT TAGCTCTGCC TTCTTTGCCA GCTGGCGGAT CGTGTATGAA GGGGGCATCG ACCCCATCCT  
 CCGGGGCTC ATGGCCACCC CTGCCAAGCT GAACCGTCAG GATGCCATGT TAGTGGATGA GCTCCGGGAC CGGCTGTTC  
 5 GGCAAGTGAG GAGGATTGGG CTGGACCTGG CAGCTCTCAA CATGCAACGA AGCCGGGACC ACGGCCTTCC AGGGTACAAT  
 GCTTGGAGGC GCTTCTGTGG GCTCTCCAG CCCCGGAATT TGGCACAGCT TAGCCGGGTG CTGAAAAACC AGGACTTGGC  
 AAGGAAGTTC CTGAATTTGT ATGGAACACC TGACAACATT GACATCTGGA TTGGGGCCAT CGCTGAGCCT CTTTGGCCG  
 GGGCTCGAGT GGGGCTCTT CTGGCTTGT TGTTCGAGAA CCAGTTCAGA AGAGCCGAGA CGGAGACAGG TTCTGGTGGC  
 10 AGAACGAGGT GTTTTACCA AAGACAGCGC AAGGCCCTGA GCAGAATTC CTTGTCTCGA ATTATATGTG ACAATACCGG  
 TATCACCAGG GTTTCAGGG ACATCTTCAG AGCCAAATC TACCCTCGGG GCTTTGTGAA CTGCAGCCGT ATCCCCAGGT  
 TGAACCTATC AGCCTGGCGA GGGACATGAG GCTTCTGCAG GAGTCTATCC CAAGTCTCCA ACTTTTGGAG ACAAGGGGAA  
 GGGGAGGACC ATGAGGCTGC CTTGTCTCCC TGGAGCAAGT GCAGGCTCGT GACGCTTCTG CTGGCTACAG CTCAGAGCTG  
 GGTTCGCCAG CCAGGAGTGA AGGCTGGGG CTCCTATCAG CAATGGACCT TCCGCTTGG GAGCCTCTTA GGTATTAGGC  
 15 TATGAATCAG GCACAGTGC AAAGGCTTGG GAGGCAAGCC ATGTGGTCTT GCACCCAGG CAAGAAAAGT CAGCTGGAGG  
 GTTACAGCA CTTTCTACTG TTCCAGGCC CTCCTCCCC TCCCTACCA TGAATAAGAG ACCACTCGGT CCTAGCCTCC  
 AGACACCCCA CAATACTCT CTGAGCCTGA GGCCAGGCAG CATGCTCTGC TTCTACCAAT AAAGCACTGC CGGAATTC-3'  
 (FRAG.NO:)(SEQ ID NO:11859)  
 5'-TC GGC CTG GTC CCG G-3' (FRAG. NO: 1727) (SEQ ID NO:11109)  
 5'-TGG GGG TTT CCG TTG-3' (FRAG. NO: 1728) (SEQ ID NO:11110)  
 20 5'-TG GTC CCG GBG BGC -3' (FRAG. NO: 1729) (SEQ ID NO:11111)  
 5'-GGC CTC GGC CTG GTC CCG G-3' (FRAG. NO:1053) (SEQ ID NO:10430)  
 5'-GGG TCT CCT CTT GTT GTT GC-3' (FRAG. NO:1054) (SEQ ID NO:10431)  
 5'- TTG CGC CTC CTG CTG GGG GT CC-3' (FRAG. NO:1055) (SEQ ID NO:10432)  
 5'-CTC TGT TCT TGT TTT GGG GGC-3' (FRAG. NO:1056) (SEQ ID NO:10433)  
 25 5'-GGG CCC GGC CGT TGT CTT G-3' (FRAG. NO:1057) (SEQ ID NO:10434)  
 5'-GTT TGG GGG TTT CCG TTG-3' (FRAG. NO:1058) (SEQ ID NO:10435)  
 5'-GGG TTC TCC TGG CCC GGG CCT TGC CC-3' (FRAG. NO:1059) (SEQ ID NO:10436)  
 5'-GGC CGT GGT CCC GGC TTC GTT GC-3' (FRAG. NO:1060) (SEQ ID NO:10437)  
 5'-CCT GTC TCC GTC TCG GCT CTT CTG-3' (FRAG. NO:1061) (SEQ ID NO:10438)  
 30 5'-GGG CCT TGC GCT GTC TTT GGT G-3' (FRAG. NO:1062) (SEQ ID NO:10439)  
 5'-GCB CCG TCC BGT GBT GCG GTB CTT GTC GCT GCB GCG CTC GGC CTG GTC CCG GBG BGC -3' (FRAG. NO:1063) (SEQ  
 ID NO:10440)

#### Human Intercellular Adhesion Molecule-1 (ICAM-1)

##### Nucleic Acid and Antisense Oligonucleotide Fragments

35 5'-GCG CGG GCC GGG GGC TGC TGG G GGT TGG CCC GGG GTG CCC C GCC GCT GGG TGC CCT CGT CCT CTG CGG TC GTG  
 TCT CCT GGC TCT GGT TCC CC GCT GCG CCC GTT GTC CTC TGG GGT GGC CTT C GCT CCC GGG TCT GGT TCT TGT GT TGG  
 GGG TCC CTT TTT GGG CCT GTT GT GGC GTG GCT TGT GTG TTC GGT TTC TGC CCT GTC CTC CGG CGT CCC CGG BGC CTC  
 CCC GGG GCB GGB TGB CTT TTG BGG GGG BCB CBG BTG TCT GGG CBT TGC CBG GTC CTG GGB BCB GGC CCC GCB GCB  
 GGB CCB GGB GTG CGG GCB GCG CGG GCC GGG GGC TGC TGG GBG CCB TBG CGB GGC TGB G-3' (FRAG. NO: 1730) (SEQ  
 40 ID NO:11112)  
 5'-GGG GGC TGC TGG G-3' (FRAG. NO: 1731) (SEQ ID NO:11113)  
 5'-T GTC CTC CGG CGT CCC-3' (FRAG. NO:1732) (SEQ ID NO:11114)  
 5'-G CCB TBG CGB GGC TGB G-3' (FRAG. NO: 1733) (SEQ ID NO:11115)  
 5'-CTC TGG GGT GGC CTT C-3' (FRAG. NO:1734) (SEQ ID NO:11116)  
 45 5'-GCG CGG GCC GGG GGC TGC TGG G-3' (FRAG. NO:1064) (SEQ ID NO:10441)  
 5'-GGT TGG CCC GGG GTG CCC C-3' (FRAG. NO:1065) (SEQ ID NO:10442)  
 5'-GCC GCT GGG TGC CCT CGT CCT CTG CGG TC-3' (FRAG. NO:1066) (SEQ ID NO:10443)  
 5'-GTG TCT CCT GGC TCT GGT TCC CC-3' (FRAG. NO:1067) (SEQ ID NO:10444)  
 5'-GCT GCG CCC GTT GTC CTC TGG GGT GGC CTT C-3' (FRAG. NO:1068) (SEQ ID NO:10445)  
 50 5'-GCT CCC GGG TCT GGT TCT TGT GT-3' (FRAG. NO:1069) (SEQ ID NO:10446)  
 5'-TGG GGC TCC CTT TTT GGG CCT GTT GT-3' (FRAG. NO:1070) (SEQ ID NO:10447)  
 5'-GGC GTG GCT TGT GTG TTC GGT TTC-3' (FRAG. NO:1071) (SEQ ID NO:10448)  
 5'-TGC CCT GTC CTC CGG CGT CCC-3' (FRAG. NO:1072) (SEQ ID NO:10449)  
 5'- CGG BGC CTC CCC GGG GCB GGB TGB CTT TTG BGG GGG BCB CBG BTG TCT GGG CBT TGC CBG GTC CTG GGB BCB GBG  
 55 CCC CGB GCB GGB CCB GGB GTG CGG GCB GCG CGG GCC GGG GGC TGC TGG GBG CCB TBG CGB GGC TGB G-3' (FRAG.  
 NO:1073) (SEQ ID NO:10450)

#### Human Vascular Cell Adhesion Molecule 1 (VCAM-1)

##### Nucleic Acid and Oligonucleotide Fragments

60 5'-CCT CTT TTC TGT TTT TCC C CTC TGC CTT TGT TTG GGT TCG CTT CCT TTC TGC TTC TTC C CTG TGT CTC CTG TCT CCG  
 CTT TTT TCT TC GTC TTT GTT GTT TTC TCT TCC TTG CTG BGC BBG BTB TCT BGB TTC TGG GGT GGT CTC GBT TTT BBBB  
 GCT TGB GBB GCT GCB BBC BTT BTC CBB BGT BTB TTT GBG GCT CCB BGG BTC BCG BCC BTC TTC CCB GGC BTT TTB BGT  
 TGC TGT CGT-3' (FRAG.NO:1735) (SEQ ID NO:11117)  
 5'-C TGT CGT-3' (FRAG. NO:1736) (SEQ ID NO:11118)  
 5'-TGC TTC TTC C-3' (FRAG. NO:1737) (SEQ ID NO:11119)  
 65 HSVCAM1AS1: 5'-CCT CTT TTC TGT TTT TCC C-3' (FRAG. NO:1074) (SEQ ID NO:10451)  
 HSVCAM1AS2: 5'-CTC TGC CTT TGT TTG GGT TCG-3' (FRAG. NO:1075) (SEQ ID NO:10452)  
 HSVCAM1AS3: 5'-CTT CCT TTC TGC TTC TTC C-3' (FRAG. NO:1076) (SEQ ID NO:10453)  
 HSVCAM1AS4: 5'-CTG TGT CTC CTG TCT CCG CTT TTT TCT TC-3' (FRAG. NO:1077) (SEQ ID NO:10454)  
 HSVCAM1AS5: 5'-GTC TTT GTT GTT TTC TCT TCC TTG-3' (FRAG. NO:1078) (SEQ ID NO:10455)  
 70 CTG BGC BBG BTB TCT BGB TTC TGG GGT GGT CTC GBT TTT BBBB GCT TGB GBB GCT GCB BBC BTT BTC CBB BGT BTB TTT  
 GBG GCT CCB BGG BTC BCG BCC BTC TCC GGC BTT TTB BGT TGC TGT CGT (FRAG. NO:1079) (SEQ ID NO:10456)

#### Human Endothelial Leukocyte Adhesion Molecule (ELAM-1)

##### Nucleic Acid and Antisense Oligonucleotide Fragments

5'-BBG TGB GBG CTG BGB GBB BCT GTG BBG CBB TCB TGB CTT CBB GBG TTC TTT TCB CCC GTT CTT GGC TTC TTC TGT C  
 CGT TGG CTT CTC GTT GTC CC TGT GGG CTT CTC GTT GTC CC CCC TTC GGG GGC TGG TGG GGC CGT CCT TGC CTG CTG G  
 GTT CTT GGC TTC TTC TGT CCG T TGG CTT CTC GTT GTC CC TGT GGG CTT CTC GTT GTC CC CCC TTC GGG GGC TGG TGG  
 GGC CGT CCT TGC CTG CTG G CCTGAGACAG AGGCAGCAGT GATACCCACC TGAGAGATCC TGTGTTTGAA CAACTGCTTC  
 5 CCAAAAACGGA AAGTATTTCAG AGCCTAAACC TTTGGGTGAA AAGAAGTCTT GAAGTCATGA TTGCTTCACA GTTCTCTCA  
 GCTCTCAGTT TGGTGTCTCT CATTAAAGAG AGTGGAGCCT GGTCTTACAA CACCTCCACG GAAGCTATGA CTTATGATGA  
 GGCCAGTGCT TATTGTACAG AAAGGTACAC ACACCTGGTT GCAATTCAAA ACAAAGAAGA GATTGAGTAC CTAAACTCCA  
 TATTGAGCTA TTCACCAAGT TATTACTGGA TTGGAATCAG AAAAGTCAAC AATGTGTGGG TCTGGGTAGG AACCCAGAAA  
 10 CCTCTGACAG AAGAAGCCAA GAACTGGGCT CCAGGTGAAC CCAACAATAG GCAAAAAGAT GAGGACTGCG TGGAGATCTA  
 CATCAAGAGA GAAAAAGATG TGGGCATGTG GAATGATGAG AGGTGCAGCA AGAAGAAGCT TGCCCTATGC TACACAGCTG  
 CCTGTACCAA TACATCTCGC AGTGGCCACG GTGAATGTGT AGAGACCATC AATAATTACA CTTGCAAGTG TGACCTGGC  
 TTCAGTGGAC TCAAGTGTGA GCAAAATTGTG AACTGTACAG CCCTGGAATC CCCTGAGCAT GGAAGCCTGG TTTGCAGTCA  
 CCCACTGGGA AACTTCAGCT ACAATTCTTC CTGCTCTATC AGCTGTGATA GGGGTACCT GCCAAGCAGC ATGGAGACCA  
 15 TGCAGTGTAT GTCCTCTGGA GAATGGAGTG CTCTTATTC AGCCTGCAAT GTGGTTGAGT GTGATGCTGT GACAAATCCA  
 GCCATGGGT TCGTGAAGT TTTCCAAAAC CCTGTGAA CCGGAAAGA TCCATGGAA CACAACCTGT ACATTTGACT GTGAAGAAAG  
 ATTTGAACCTA ATGGGAGCCC AGAGCCTTCA GTGTACCTCA TCTGGGAATT GGACAACGA GAAGCCAACG TGTAAAGCTG  
 TGACATGCAG GGCCGTCCGC CAGCCTCAGA ATGGCTCTGT GAGGTGCAGC CATTCCCCTG CTGGAGAGTT CACCTTCAAA  
 TCATCTCGTA AGTCCACCTG TGAGGAAGGC TTGATGTTGC AGGGACCAGC CCAGGTTGAA TGCACCATTG AAGGGCAGTG  
 GACACAGCAA ATCCAGTTT GTGAAGCTTT CCAGTGCACA GCCTGTGCA ACCCGAGCG AGGCTACATG AATTGTCTTC  
 20 CTAGTGCTTC TGGCAGTTTC CGTATGGGT CCAGCTGTGA GTTCTCTGT GAGCAGGGTT TTTGTGTGAA GGGATCCAAA  
 AGGCTCCAAT GTGGCCACAG AGGGGAGTGG GACAACGAGA AGCCACCATG TGAAGCTGTG AGATGCGATG CTGTCCACCA  
 GCCCCGGAAG GGTGTGTGA GGTGTGCTCA TTCCCTATT GGAGAATTCA CCTACAAGTC CTCTGTGCC TTCAGCTGTG  
 AGGAGGGATT TGAATTATAT GGATCAACTC AACTTGAGTG CACATCTCAG GGACAATGGA CAGAAGAGGT TCCTTCTCAG  
 CAAGTGTGTA AATGTTCAAG CTTGGCAGTT TCAACATGAG CTGCACTGGG GAGCCCGTGT TTGGCAGTGT  
 25 GTGCAAGTTC GCCTGTCCTG AAGGATGGAC GCTCAATGGC TCTGCAGCTC GGACATGTGG AGCCACAGGA CACTGGTCTG  
 GCCTGTCTAC TACCTGTGAA GCTCCCACTG AGTCAACATC TCCTTGGTA GCTGGACTTT CTGCTGTCTG ACTCTCCCTC  
 CTGACATTAG CACATTCTT CCTCTGGCTT CGGAAATGCT TACGGAAAGC AAAGAAATTT GTTCTGCCA GCAGCTGCCA  
 AAGCCTTGAA TCAGACGGAA GCTACCAAAA GCCTTCTTAC ATCCTTTAAG TTCAAAAGAA TCAGAAACAG GTGCATCTGG  
 GGAACCTAGAG GGATACACTG AAGTTAACAG AGACAGATAA CTCTCTCGG GTCTCTGGCC CTCTGTGCT ACTATGCCAG  
 30 ATGCCTTAT GGCTGAAACC GCAACACCCA TCACCACTTC AATAGATCAA AGTCCAGCAG GCAAGGACCG CCTTCAACTG  
 AAAAGACTCA GTGTGCCCT TCCTACTCT AGGATGTTGC AATGTGTGGC TAATGAAGGG AAAGGATATT TTCTCCAGG  
 CAAAGGTGAA GAGACCAAGA CTCTGAAATC TCAGAATTCC TTTTCTAACT CTCCCTGTGCT CGCTGTAAA TCTTGGCACA  
 GAAACACAAT ATTTTGTGGC TTTCTTCTT TTGCCCTTCA CAGTGTTCG ACAGCTGATT ACACAGTTGC TGTCTAAGA  
 ATGAATAATA ATTATCCAGA GTTTAGAGGA AAAAAATGAC TAAAAATATT ATAACCTTAA AAAATGACAG ATGTTGAATG  
 35 CCCACAGGCA AATGCATGGA GGGTGTGTA TGGTGCAAT CCTACTGAAT GCTCTGTGCG AGGGTACTA TGCACAATT  
 AATCACTTTC ATCCCTATGG GATTGAGTGC TTCTTAAAGA GTTCTTAAAG ATTTGTATAT TTTTACTTGC ATTGAATATA  
 TTATACTCT CCATCTCTT TCATTCAATA CAAGTGTGGT AGGGACTTAA AAAACTTGTG AATGCTGTGA ACTATGATAT  
 GGTAAAGATT ACTTATTCTA GATTACCCCT TCATTGTTTA TTAACAAAT ATGTTACATC TGTTTTAAAT TTATTTCAAA  
 AAGGGAACCT ATTTGCCCCT AGCAAGGCAT GATGTTAACC AATGATAAGT TCTGAGTGT TTTACTACAG TGTGTTTTG  
 40 AAAAGACTGA AGTATGGAG AGTAAAAACT GTATGGAAG TTTGTATATT GTCAGATATT TTTTCAGAAA TTTCTGGGTT  
 CCACGATGAA AAACCTCCAT GAGGCCAAAC GTTTTGAAC TATAAAAGCA TAAATGCAAA CACACAAAGG TATAATTTTA  
 TGAATGTCTT TGTGGAAAA GAATACAGAA AGATGGATGT GCTTGTGATT CCTACAAAGA TGTGTGACAG ATGTGATATG  
 TAAACATAAT TCTGTATAT TATGGAAGAT TTTAAATTC CAATAGAAAC TCACCATGTA AAAGAGTCAT CTGCTAGATT  
 45 TTTAACGAAT GATGATGTCT AATAGTTATT CCCTATTGTT TTCTTCTGT ATGTTAGGGT GCTCTGGAAG AGAGGAATGC  
 CTGTGTGAGC AAGCATTAT GTTTATTTAT AAGCAGATT AACAATTCCA AAGGAATCTC CAGTTTTCAG TTGATCACTG  
 GCAATGAAA ATTTCTCAGT AGTAATTGCC AAAGCTGCTC TAGCCTGTAG GAGTGTGAGA ATCAAAACTC TCCTACACTT  
 CCATTAACCT AGCATGTGTT GAAAAAATAA GTTTCAGAGA ATTCTGGCT GAACACTGGC AACGACAAAG CCAACAGTCA  
 AAACAGAGAT GTGATAAGGA TCAGAACAGC AGAGGTTCTT TTAAGGGGGC AGAAAACTC TGGGAAATAA GAGAGAACA  
 50 CTACTGTGAT CAGGCTATGT ATGGAATACA GTGTTATTT CTTTGAATTT GTTTAAGTGT TGTAAATATT TATGTTAACT  
 GCATTAGAAA TATGCTGTGT GAAATACAG TGTGTTTGT GTTTGAGTTT TATTGAGAA TTTAAATATT AACTTAAAT  
 ATTTTATAAT TTTTAAAGTA TATATTTATT TAAGCTTATG TCAGACCTAT TTGACATAAC ACTATAAAGG TTGACAATAA  
 ATGTGCTTAT GTTT GATCAAAAT TTTACTTAT ATGCATTGTA TATATAATA AGTATATAAA TGCACACACA GACACAGCAA  
 TGTGGTGAA CAGTCTTAT ACAATTATAT GGATGAAATG CATAAAATGC TGAGTTAAAG AAATCAGACC AAAGAACATA  
 55 TACTGAAAGA TTCTCTCTAT ATACAAAGTT CAAAAATAGG TGGACCAATT CATGGTGGTG TTGAAATCA GAAGAGAGGC  
 TACCTTTGTG GGGAGGGGAC AGTTTAAATG CCAGAAGCGG TAAATAAGGA ATCCTCTGGG GAGTGGTAAT GATCTGGATG  
 CTGGCTACAG GATGTGTGG TTGTAAAAAT GCATTTTTTT ATACTAGCT TTTTCCATGT GTATATTATA CTTCAAAGAA  
 GTTCAGTTAA TAATTTCTCA TGTCACTGTA GAGTAGCTCA GTTAGCCCCA GCAAGCCTCT GGCCTTAATCT GTTTTACCT  
 TAAGCCATCA GTCATTTACA AGTAGGAAAA TTCACAGGGA AAGTTAGAGT ATAAATCCA GAATGAAGGT TTAAGGGTA  
 60 AGAGTCTCTC CATTTTCCAA AGCCCGTTTA TTTCTTGATT CCAGTCTTCA AGAAGTCTCA GCATTGTGTG TTTTTCATGT  
 ATCTTACAAG AAGACAGCAT GTGCTTCTAA CACCTGATAC ATTGTATCTA CCAGCACTTG GTAAACAGAA AAGAACCACA  
 TTTTCTTGT AGGAGAAAT TGGTGCCAT TTTCTACCAG GCACCAATAA GTGGGACCAA TAGGTGGGAT TAAAGATACA  
 GTAGAAAGTA TTTAAACTT GCCAGGGGGC AATAGTCTGA AAATAAGTAA ATTTGTGCTA TAGAATGGAA GTTACAGGCT  
 TCTTTCTTTT TTCCACAAG ATCTGTCTCT TGAGCCCTTA GAGACTTTTC TGTCTGTTAC TGTCTCTCA TTCTCATCT  
 65 GCAGAGCCAG CCTGAGAAG TGCAGACCAA AGCCAGGGA GGTCTGCAA AGATGTACAA ATGGAAGTCA CCTTAATAAC  
 CTCTGACTGC TGCGCATAAT ACATTTCACT CAAAAGAGGG GTTAAACAAT GGAACAGAA ACAGAGGCCA GAAATAATGC  
 TGAACACTGA CAACCATCTG ATCTTTGACA AAATCCACAA TAAACAAGG TGGAGAAAGG ACTCCTATT CCATTAATGTT  
 GCTGGGATAA CTGTCTAGCT ATATACAGAA GATTGAACCT GGGCCCTTC CTTACATCAT ATACAAAAA TAACTCAAGA  
 TGGAGTAAAG ACTTAAATCT AAAACCAAAC ACTATAAAAC CCTGTGGAAG TAGCCTGGGA AATACCATTC TGGACATAGG  
 70 ACCTGGGAAA GACTTCAATG CAAGACACCA AAGCAAAATG CAAACAAAAC CAAATGACT AATGAAACTA ATGAAACTCT  
 TTAGTTGTAC AACAGATAGT TTATCTGTAC AAAAAATAA ACTATCAACA GAGTAAACAA CCTACAGAA GGAATAATTT  
 TTTGCAACT ATGCATCTGA CAAAGGTCTA ATATCCAGAA TCTATAAGGA ATTTAAACAA ATTTACAAGC AAAAAATGA  
 CCTCAATAA AAGTGGGCAA AGGACATGAA CAGATGCTTT TCAAAATAAG ACATTCACAC ATCCAACAC CATATGAAAA  
 GATGTTTAA ATCACTAATC ATTAGAGGAA TACAAATCAA AAGCATAATA AGATACCATC TAATACCACT AGGAATGACT  
 ACTATTAATA AGTCAGACAA TAACAGATGC TGTGGAAGGT TGTGGAGAAA AGGGAATGTT TATGCACTGC TAGTGGGAAT  
 75 GTAAACTAGT TCAGCCATTG TGAAGAGAG TGTGGTGATT CCTCAAGAA TGTAACCCG AACTGCCTTT CAATCCAGCA

ATCCCAATTAT TGGATATACA CCAAAAGGAA TAGAAATTGT TTTACCGTAA AGGCGCATGC ATGCATATGT TCATTACAGC  
 ACTATTTTACG ATAGCAAAGA CATGGAATCG TCTAAATGCC CATCAGTGGT AGACTAGCTA AAAAAAAAAA AATGTGGTAC  
 ATATACATCA CAGAATAGTA TGCAGCCATA AAAATGAACA AGATCATCAT GTCCCTTGCA GCAACATGGA TGTAGTTGGA  
 5 GGCCATTATC CTAAGCAAAAT TAATGCAGGA ACAGAAAAGC AAATACCACA TGTCTCAT TATAAGTGAC AGCTAAATAT  
 TGAATACACA TGGACACAAA GAAGGGGAACA ATAGACATGG GACCTACTTG AGAATAGAGG GTGGGAGGAG GGTGAGGATC  
 AAAAAAGTACC CATAGGACAC TGTGCTTATT ACCTGGGTGA TGAATAAATT TGCACACCAA ACCCCTGTGA CACACAATTT  
 ACCTATATAG AAAACCTGTG CATGTACCCC TGAACCTAAA AGTTAATGGT GGGGGGGTGG GGTTAAGCTA CTTTGTGGTA  
 TAAATCTGAG CATTCATATT AAAATAAAAA ATTTACCTCA TTAGAGTAAT TAACATTTAT TAAGCAAAGA GCCAAGTACC  
 10 TTACACACAT GATGTTTAAAT CTCACAATGA TCTTAAATCT CATAACAACC GTCCATTGTA TGTACATATG TGGAAATTGA  
 GCCTTGGAGA GTTTAAATGC ATGGGGCATG CCAATTGACT AGAACTGGA AGCATCAGGA TTTAAACTCA GTTCTGAATG  
 GTTTGTAGG CTTTGTTTT TCCACATTAT AGCATGGCCT GCCATGAAGA ACAGGTCCCT TCTGGTGT TGTCTGTGTG  
 GTTTAAGTGA AGCAAATATT TATTTAAATA TTCAAGATAT GCTGTAAAT TTTTACTCAA AAATTTGAGT ACAGTATGGA  
 TCTTCTGAAG CCAATAAAT CTTATTCAAT GCTTAAGTTGA GAAATTTTAT GGAGTAGTTC TCAATTTT TAAGTTTCCA  
 15 CTGCAAGGTT AAGTCTATG GAAAGATTCA CTGTAAATTT TTTTCTCAT TTGGACATCA GCTTTTCT TCCCTCAGAC  
 CCGCTGAAAG ATAATTTTAA AAATAAAAAA CTTGTTTTTA TATCAAGTGG GGACATTTT TCCAAATGAA AACCGTGTAT  
 TCATTTTATA TGATAAAATC AATGTTATTA TTTTAAAAAT TTGATTTAA AAATCATTAA AAATAAATTT TCAGATATTA  
 CCTGAAATTC TACCATCCAG AGATAATAGT GCTTAAAGAT TTGATATATA GACACACACA CATATATACA TATATATCAT  
 CCTAAACCTC TTGTATATAA TGTATATAAA GTTTTAAATA AAAAATAGGA GATTAATGCC CTTTGAATGA AAAATAATAC  
 20 AATGTGTATG CTTTAAATC TGGCCTTTAC TTTATAACAT TTATCAGAGC AGTCATGAGA TAATGATTTA CATGTCATT  
 GTTAGTAAGC TAATAGCTAA GTGCATGAAC TCTGGAGCTA GCCTCCCTGG ATTTTAAATCC CAGATCTGTC ACTGACCAGC  
 TGAGCAATAC TAGGTAAAT GCTCTGTCT GCTCTGTCT TATGATGGCC ACTTAAACAAC AATGCCITCA CATACTGAAC ACAAATATAC  
 GGATTTGGT GAGCATTTAA TGAGCATACG TATGTAGGCC ACTTAAACAAC AATGCCITCA CATACTGAAC ACAAATATAC  
 GAGCTGTGT CTTATTGGGC TCATGTTTTT CCTACCCTA AGCCGCATGC ATGCAAGGAC CATGTTGGT TGTGTTCCCA  
 25 TTGCATCCCC AACCTGGTAT ACAGTGTGCA TTCAATAGTT GTTGACTATT ATTACTAGTG GCATTTAACA AATATCTGTT  
 AAATGAGTGA AGAAATACCC ATTTACTGCA AGTGTGTCTA ATATTGATGG CATAATGGGG GAAACTCAAA CTCTGGAGTC  
 AAACAGGTTT TAAAACCTTA TTCCCTCATC CTCAGTATT GAGCTTTTTT TTTTGGCAGG TGTGTGTGTG GGACAACTTA  
 TTGAATTTTT CTGAATTTCC AGCTTCGCAT ATATAAAATA GACATAGTGA TTCACTCTTG CAATGTATGG ATTTGAGACA  
 ATTGTGTAAG TTTATCAATA AATAGTAGCT ATTTTGTAT AAGTATTACA TATAATATCC AGGCCACTGC TTTGCATAAC  
 30 CCAAAAGGGG CACCATTCT GCAGAATACA ACATAAATGG TTGCCCTGGA GCAGTGCACT ATAGGAACCC TGAGGGGACC  
 TACAGTATG TTTATAGTT ATAGATTACA AATTATCCCT TCTCAGAGT CTCTCAAGGT TGGATGTATT TGAGTGCAT  
 AAGAGCAATT TAGGATTAA AGTAGCTGCA GAAACCATCT GCAGTGATAT TCTCATTTTA AATCCGCGGG AAAGAAGACA  
 GCTATAAACT TGGGACCTGG GTTTAAGCAT TTTAAATGCC AAGTTCACCA TTTTCTAAAA CACAACAAAT ACCCAGTGAG  
 AGAGGGAGAA GGAAGTAAA TGCCTCTGAA TAAGCAAGTT AATGTCAGTA GTTGTACTGT ATGCATATTG ATGAACAATA  
 35 GAGGAACCAA TGGCCAATG GATGAGCAGG ATATTGGTCA ATAACAAGTT GCCTTTGAGG AAAAAATGATT TTCTTGGCAA  
 GTTCTTTATC AGCATTACAA AGCTAAAAGC TACGCTTATC ATCACTTATA CTAGCATACC CTGTTGTGCA AATGCTGTCT  
 GTGTTTGCAT CTGCTATTGT TGATGCCCTG TGCATGAATC AGGACTCCAG CCCACAAGTT TTCCCAAGAC TTTCTTATGG  
 CCATCATCTT TAAGTGTCTG GTGAACATC ATAGTTTGGT ACACAAAAGG GTCAACCTGG GTGATGGCTA GGTGTTGACT  
 CAGTCGTTAC ATTTCAATAG AGCAGGAAGG GGAATGTGTG GCCTGTAACC TCAGGGAATT TTGCCAGTTG GTCCACCCCA  
 40 CTCTCTCTCT CCGTCTCTGA GGAAGTGGCA CAGCCTAGAA CAGCACCCACA GGTGAGAGAA ATGCAAAACC TAACAGAGA  
 AGCAACTCTT TTGCCAGTAG TAATAGTTCA GGACCCACAC CAGCTTTTAT TAAAAATTTT AATAACACTC AAGTATTGGC  
 AGAAAGAAAT AATCTTGGGT TAACTATAAC TAGAATATTG ACTCTTCTC TGTGGAAGAA TCAGCCAATC ACATTTGTTT  
 ACATCAGTTC CCTGGAAGAA GAAAAATACA CTGATGTGCG AAGAGACAA ATTTAAGCTA GATGTAAATA ACTTCTTTA  
 45 CCGTGTATG CTAGGCTAT TACATATTGG AACTATTTT TCAGGGAAGA ATTGTGTAGG GTTTCAGGGA AGAATCTGGA  
 AGAAATATA GAGCTGAAAT GATCTTGCA GCTCACTGAAA CTGCAAGGTT TAGATCCACA CTGATACTCG TTCTATTATC  
 ACTGTAATGA AGGCTGATGG AATAAGTAAA AATGTTTTGT ATTAGTATGT TTTTACACT ATTGCAAGG CATAAATAGG  
 TTAGGTTTTG ATCTTAATTT AATTCTAACA TGTATTGTG ACAAGCTGTG AGCAGTTTTC AGGAGTTAGG TATCTGGCCA  
 TGACTGATTT TTACAGGTTT AATCATCTGG TAGAAGGGTC ATACACAATA GGAAGATGTG TGTGACAGGT TTGTATCATT  
 50 ACTATAATCA CACAGAGAGC TGTAGAATTT TAGGCTGGCA GGGTGGCTCA CGCTGTAAAT CCCAGCACTT TGGGAGGCCA  
 AGGCAGGCGG ATCAAGAGGT CAGGAGATGG AGACCATCTT GGCTAACACG GTGAAACCCC GTCTGTACTA AAAATACAAA  
 AAAAAAAGAA AGCCAGGCTT GGTGGTGGCG GCCTGTAGTC CCAGTACTT GGGAGGCTGA TGGCGTGAAC TGCGTGAAC  
 CCGGAGGTTG GAGCTTGCAG TGAGCCGAGA TCGCATCACT GCAATCCAAC CTGGGCGACA GAGGGAGACT CAGTCTCAAA  
 AAAAAAAGAA AAAAAAAGTC ATGTTAGATC CAGAGGGGTA GCAACTGGGG CTGGGCTGTC AGTCAACTCA GTCAACTCAG  
 55 TCAACTCTGC TCCCCAGAG GAGATGCCAG TGATGCATTT TCAATGGCAA CATTTGCAGT CAGCATCAIT GATTAATCTC  
 TGATTATAGA GACACAGCTG CAAACGATTC CCCATTAAT ATGATGTTTC TTGCAATGTT TGGAGGTGAC TCCTTTTATG  
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 CCTGGGGTTG CCGTAACAAG TTACCACAAA CTAGGTGGCT TAAACAATA GAATTTTATT CTCTCAGATT TCTAGAGGCA  
 70 GAAGTTCACA GTGTGCTAG AGGGCCATGT TCTCTGAGG GCTTTAGGGG AGAATATATT TCATATCTT CTCTAGCTT  
 CTGGGTGTC CTGGCAATCC TTAGCTTACT TTGGCTTTCT GTGCTTCTAC ATCATCTTTT TATAAGAACA CCAAGTATAG  
 TGATTAAGGG CATACCTTAC TTTAATATGA CCTCATTTA ACTAATTATG TCTTCAATAA CCCTATTTCC AAATAAGGCC  
 ACATTCTGAA GTATTGGGAG TTAGAACTTA AAGCTTTTTG GGAGGACAC AGTTCAACCC ATAACAACC CTAAAACTGA  
 TATTTATCT CAATTAAAGT TTGAAATGTT TTTTAAAAA AGAATATTCT ATTAGAGTTT TTAATGTATA GTTTTAAACAT  
 75 ATAGTTCTTT AGCCCCAAT TTTTTTTTT TTTTTTTTT TTTTTTTTT TTTTGTAGAC GGAGTCTGCG TCTGTGCCCC  
 AGGCCGGACT GCGGACTGCA GTGGCGCAAT CTCGGCTCAC TGCAAGCTCC GCTTCCCGG TTCACGCCAT TCCCCTGCT

CAGCCTCCCG AGTAGCTGGG ACTACAGGCG CCTGCCACCG CGCCCGGCTA ATTTTITGT ATTTITAGTA GAGACGGGGT  
 TTCACCTTGT TAGCCAGGAT GGTCTCGATC TCCTGACCTC ATGATCCACC CGCCTCGGCC TCCCAAAGTG CTGGGATTAC  
 AGGCGTGAGC CACCGCGCCC GGCCTGCCCC CAATTATTTA GTTTTCTAT AAACAGGGAA ATTTATTGT GTGGCCCTTA  
 5 GAACAAATTT AATTTCCACT CTAATTCCTA CTTATGTGTA TATAATGCTT TTAGAAATTT GTATTATTCA GAAATAAAC  
 ATATACTATT GTATCTGTG CCTACACTTA GATTTTATG CCTGCTATAT TTAATTTTA TTAGTATTT AATTGTTTTA  
 TTAAAGAAAG AATGTGCTG TAATCTCAGC ACTTTTGAGA GGCCAAGGCA GAAGGATTGC TTGAGCCAG GAGTTTGAGA  
 CCAGACTGAG CAACACAGGG AGACCCCAT CTCTACAAA AATAAAAAA TTCTCCAGGC CTCATGGCAC ATACCTGTAG  
 TTCTAGTTAC TTGGGAGACT GGGGTGGGAG GATGCATTGA GCCCAGGAGA TTGAGGCTGC AGTGAGCCAT GATCAGGCCA  
 10 CTGTACTCCA GCTTGGACAA CAGAGTGAGA GCTTGTCTAG ATAGATAGAT AGATAGATA TCTAAATAGA TAATAGACAG  
 ATTATCTAAA TAGATAATAG ACAGATTATC TAAATAGATA ATAGACAGAT TATCTAAATA GATAATAGAC AGATTATCTA  
 AATAGATAAT AGACAGATTA TCTAAATAGA TAATAGACAG ATTATCTATC TAAATAGATA ATAGATTATC TAAATAGATA  
 ATAGATAGAT AGATTAGATA GATAGATAGA TAGATAGAGC TTGGACAACA GAGTGAGAGC CTGTCTAGAT AGATAGAAAC  
 AAAGAAAGAA AGAAAGAATG GTGCTCATAT TTTAAAGCAT TGAAAAATGG TCTTCCTTGC TTATATTACC CACACCTTCT  
 TTGTGGCAT TAAGATGCAA ACTTTGTTTT AAACAGTTGA GTAAATCAAA GATGGGACTG TTAAGTTATT TGTGTTATTT  
 15 ACCTGCTTTT TGAATAATGA AAAATAAAAC TCTAGGTTTA ATTAGTAGTA TGCTATTIAG TAATGAAGTA AAGCTAGAGG  
 CTTGGAACAA ATCTTGTGTA ATTTCTCTTT GAATGAGAGA GAAATTTTAA AGTAAGCAA CAAATAAGTT GTGTGTCACC  
 ACTCATTCAG TCATTAAACA AGTATTCCA GAGTACTTAT TCTGTGCCAG GAAATGTGT AGGTGCCCTC AACAACTTAG  
 AGCTAGCCCT GAGACACAAG TAAGTAGGTA TATTATTATG AATGGTATGA TCTTTGGAGG ACTGGGTATT GGCTAGCTCA  
 20 TGGGAGTACA AGATAGGTAC CCAGTGATGA AGTCAGGAAA GGTTCCTTAT GGTGATATGA TGACGTCTAT GCTGATTATA  
 AGGTAGTGT AGAATAAACT TTGTGCTTTT AAAATTGCAT AGCACTGTAT TAGAGAGTTC ATCTTCAAAA TAATCGAAAA  
 GGCTGAGTGT GTGAGCCCAT GGCTGTAATC CCAGCACTTT GGGAGGCCGA GGTGGGCAGA TTGCTTGAGC TAGGAGTTGC  
 AGACCAGGCT GGCCAACATG GTGAAACCCC GTCTCTACTA AAAATACAAA AATTAGCCAG GAGTGATGGT GCGCACCTGT  
 AATGCCAGCT ACTTTGGGAG CTGAGGCAGG AGGATCACTT GAACCCAGGA GGTGGAGGTT GAAGTAAGCC GAGGTATGTC  
 25 CACTGCACTC CAGCTTGGGC AACAGAGTGA GACTCCATCT CAAAAAATAA AAAAATGATC AAAGAAAGGT GAATTTTCAT  
 CTACCTTATT TCTGCTGAGG AAAATGGACT ATTTTCAAT ATTTTAAATA AGGTCAAAA TGAGGGATC-3' (FRAG.NO.)(SEQ ID  
 NO:11849)  
 5'-CCTGAGACAG AGGCAGCAGT GATACCCACC TGAGAGATCC TGTGTTTGAA CAACTGCTTC CAAAAACGGA AAGTATTTC  
 AGCCTAAACC TTTGGGTGAA AAGAACTCTT GAAGTCATGA TTGCTTCACA GTTCTCTCA GCTCTCACTT TGGTGTCTT  
 30 CATTAAAGAG AGTGGAGCCT GGTCTTACAA CACCTCAAG GAAGCTATGA CTTATGATGA GGCCAGTGCT TATTGTCAGC  
 AAAGGTACAC ACACCTGGTT GCAATTCAAA ACAAAAGA GAATGAGTAC CTAACTCCA TATTGAGCTA TTCACCAAGT  
 TATTACTGGA TTGGAATCAG AAAAGTCAAC AATGTGTGGG TCTGGGTAGG AACCCAGAAA CCTCTGACAG AAGAAGCCAA  
 GAACTGGGCT CCAGGTGAAC CCAACAATAG GCAAAAAGAT GAGGACTGCG TGAGATCTA CATCAAGAGA GAAAAAGATG  
 TGGGCTGTG GAATGATGAG AGGTGCAGCA AGAAGAAGCT TGCCCTATGC TACACAGCTG CCTGTACCAA TACATCTGTC  
 35 AGTGGCCACG GTGAAGTGTG AGAGACCATC AATAATTACA TTGCAAGTG TGACCCCTGGC TTCAGTGAGC TCAAGTGTA  
 GCAAAATTGT AACTGTACAG CCCTGGAATC CCCTGAGCAT GGAAGCCTGG TTTGCAGTCA CCCACTGGGA AACTTCAGCT  
 ACAATTCTTC CTGCTCTATC AGCTGTGATA GGGGTATACCT GCAAGCAGC ATGGAGACCA TGCAAGTGTAT GTCTCTGGA  
 GAATGGAATG CTCTTATTC AGCCTGAATG GTGGTTGATG GTGATGCTGT GACAAATCCA GCCAATGGGT TCGTGAATG  
 TTTCCAAAAC CCTGGAAGCT TCCCATGGAA CACAACCTGT ACATTTGACT GTGAAGAAGG ATTTGAACCTA ATGGGAGCCC  
 40 AGAGCCTTCA GTGACTCTCA TCTGGGAATT GGGACAACGA GAAGCCAACG TGTAAGAGCTG TGACATGCA GGCCTGCCG  
 CAGCCTCAGA ATGGCTCTGT GAGGTGCAGC CATTCCCTG CTGGAGAGTT CACCTTCAAA TCATCTCAGC ATCTCACCTG  
 TGAGGAAGGC TTCTATGTGC AGGGACCAAG CCAGGTGTA TGCACCACTC AAGGGCAGTG GACACAGCAA ATCCCAGTTT  
 GTGAAGCTTT CCAGTGCACA GCCTTGTCAC ACCCCGAGCG AGGCTACATG AATTGTCTTC CTAGTGCTTC TGGCAGTTTC  
 CGTTATGGGT CCAGCTGTGA GTTCTCTGT GAGCAGGGTT TTGTTTGAA GGGATCCAAA AGGCTCCAAT GTGGCCCCAC  
 45 AGGGGAGTGG GACAACGAGA AGCCACATG TGAAGCTGTG ATGATGCGATG CTGTGCCACCA GCGCCGGAAG GTTGTGGTGA  
 GGTGTGCTCA TTCCCTATT GGAGAATCA CCTACAAGTC CTCTGTGTCG TTCAGCTGTG AGGAGGGATT TGAATTATAT  
 GGATCAACTC AACTGTAGTG CACATCTCAG GGACAATGGA CAGAAGAGGT TCCTTCCTGC CAAGTGGTAA AATGTTCAAG  
 CCTGGCAGTT CTGGGAAGA TCAACATGAG TGCAGTGGG GAGCCCTGTG TTGGCACTGT GTGCAAGTTC GCTGTGCTG  
 AAGGATGGAC GCTCAATGGC TCTGCAGCTC GGACATGTGG AGCCACAGGA CACTGGTCTG GCCTGCTACC TACCTGTGAA  
 50 GCTCCCACTG AGTCCAACAT TCCCTTGTA GCTGGACTTT CTGCTGCTGG ACTCTCCCTC CTGACATTAG CACCTTTCT  
 CCTCTGGCT CGGAATGCT TACGGAAAGC AAAGAAATTT GTTCTGCTGCA GCAGCTGCAA AAGCCTTGA TCAGACGGAA  
 GCTACCAAAA GCCTTCTTAC ATCTTTAAG TTCAAAAGAA TCAGAAACAG GTGCATCTGG GGAAGTAGAG GGATACACTG  
 AAGTTAAACG AGACAGATAA CTCTCTCGG GTCTCTGGCC CTCTTGCCT ACTATGCCAG ATGCCCTTAT GGCTGAAACC  
 55 GCAACACCCA TCACCACTC AATAGATCAA AGTCCAGCAG CCAAGGACCG CCTTCAACTG AAAAGACTCA GTGTCCCTT  
 TCCTACTCTC AGGATCAAGA AAGTGTGGC TAATGAAGGG AAAGGATATT TTCTTCCAAG CAAAGGTGAA GAGACCAAGA  
 CTCTGAAATC TCAGAATTCC TTTTCTAAT CTCCCTTGCT CGCTGTAAAA TCTTGGCACA GAAACACAAT ATTTTGTGGC  
 TTTCTTTCTT TTGCCCTTCA CAGTGTTCG ACAGCTGATT ACACAGTTGC TGTCTAAGA ATGAATAATA ATTATCCAGA  
 60 GTTTAGAGGA AAAAAATGAC TAAAAATAT ATAACCTTAA AAAATGACAG ATGTGGAATG CCCACAGGCA AATGCATGGA  
 GGGTTGTATA TGGTGCAAT CTTACTGAAT GCTCTGTGCG AGGGTTACTA TGCACAATT AATCATTTC ATCCCTATGG  
 GATTCAAGTC TTCTTAAAGA GTTCTTAAAG ATTGTGATAT TTTTACTTGC ATTGAATATA TTATAATCTT CCATCTTCT  
 TCATTCAATA CAAGTGTGGT AGGGACTTAA AAAACTGTGA AATGCTGTCA ACTATGATAT GGTAAAAAGT ACTTATTCTA  
 65 GATTACCCCC TCATTGTTA TTAACAAAT ATGTTACATC TGTTTTAAAT TTATTTCAAA AAGGGAAACT ATTGTCCCT  
 AGCAAGGCAT GATGTTAACC AGAATAAAGT TCTGAGTGT TTTACTACAG TTGTTTTTGG AAAACATGGT AGAATTGGAG  
 AGTAAAAACT GAATGGAAGG TTTGTATATT GTACATATT TTTTCAGAAA TATGTGGTTT CCACGATGAA AAACITCCAT  
 GAGGCCAAC GTTTTGAAC AATAAAAGCA TAAATGCAAA CACACAAAGG TATAATTTTA TGAATGTCTT TGTGGAAAA  
 70 GAATACAGAA AGATGGATGT GCTTTGCATT CCTACAAAGA TGTTTGTCAG ATGTGATATG TAAACATAAT TCTGTATAT  
 TATGGAAGAT TTTAAATCA CAATAGAAAC TCACCAATGTA AAAGAGTCAT CTGGTAGATT TTTAACGAAT GAAGATGTCT  
 AATAGTTATT CCCTATTGT TTTCTTCTGT ATGTTAGGGT GCTCTGGAAG AGAGGAATGC CTGTGTGAGC AAGCATTAT  
 GTTTATTAT AAGCAGATT AACAAATCCA AAGGAATCTC CAGTTTTCAG TTGATCACTG GCAATGAAAA ATTCTCAGTC  
 75 AGTAATTGCC AAAGCTGCTC TAGCCTTGAG GAGTGTGAGA ATCAAAACTC TCCTACACTT CCATTAACCTT AGCATGTGT  
 GAAAAAAGAA GTTTCAGACA AGTTCTGGCT GAACACTGGC AACCAACAG CCAACAGTCA AAACAGAGAT GTGATAAGGA  
 TCAGAACAGC AGAGTTCTT TTAAGGGGCG AGAAAAACTC TGGGAAATAA GAGAGAACAA CTACTGTGAT CAGGCTATGT  
 ATGGAATACA GTGTTATTTT CTTTGAATTT GTTTAAGTGT TGTAAATATT TATGTAACCT GCATTAGAAA TTGCTGTGT  
 GAAATACAG GTTGTGTTGT TATTGAGATT TTTAAATTAT AACTTAAAA ATTTTATAAT TTTTAAAGTA  
 TATATTATT TAAGCTTATG TCAGACCTAT TTGACATAAC ACTATAAGG TTGACAATA ATGTGCTTAT GTTT-  
 3'(FRAG.NO.)(SEQ ID NO:11848)

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5-TCT GGC CTG TCC GCC GGC TCT TCG GTG GCT CGG CCC CGC TCC TTG TCT TGC CGC GGG TTG GTT CCT GGG CCT GGT  
TCT TGC GGG CGT TTC GGT CTG CTG GCT GGT CTG GGC CCG CGG TGC GGC GGG TGG CTT GCT GTT CTG CCT GGG CTC TCC  
CCT CTC CTC CTT TTC TCC CTT CCT CTG TCT TGC CTC CTT CCT CTG GGT CCG CTT GGC CTG GGC GCT CTT CCC CTC GGG  
CGG CTG GGC CGC CTC GTG CTG CCT GGT CCG CTC CTT GGC GGT GCT CTT TCC CTT TCC CCG CTC GTG GGG TTT GCG GGG  
CTG GGC TGC CTT GGG GGG TCT GGG CTT TTT GGG GCT GGC TGG CTT CTG CTT GCG GGC GCG TGG GCT TCC CTG TGC CCC

5 5'-TCTGCGC-3' (FRAG. NO: 1757) (SEQ ID NO:11139)  
5'-CCT GCT CCT GGG G (FRAG. NO:1758) (SEQ ID NO:11140)  
5'-CTGCGCGCCCTGCTCC (FRAG. NO:1108) (SEQ ID NO:10486)  
5'-CGCCCGGCTTCTCT (FRAG. NO:1109) (SEQ ID NO:10487)  
5'-CGTGTGGGCTTCGG (FRAG. NO:1110) (SEQ ID NO:10488)  
5'-CCCCGCGCCTCGGTTGTCTC (FRAG. NO:1111) (SEQ ID NO:10489)  
10 5'-TGCTCGCTGGGCTTG (FRAG. NO:1112) (SEQ ID NO:10490)  
5'-GGTTTCTCGGGCCCTGGGTTTC (FRAG. NO:1113) (SEQ ID NO:10491)  
5'-TCTGCCGGGTCGTTTTC (FRAG. NO:1114) (SEQ ID NO:10492)  
5'-GGGTGCTGGCTGCG (FRAG. NO:1115) (SEQ ID NO:10493)  
5'-CTTGGTGCTGGGGCTCC (FRAG. NO:1116) (SEQ ID NO:10494)  
15 5'-GGCGGCTCGGGGCTGGGTTGGG (FRAG. NO:1117) (SEQ ID NO:10495)  
5'-CTTGGCTGGTTCCTGGCCTCGGG (FRAG. NO:1118) (SEQ ID NO:10496)  
5'-CCTCCTCCTCCTCCTCGCTCCCTTTTCTTCCTCT (FRAG. NO:1119) (SEQ ID NO:10497)  
5'-TCCCTGCTGCTCTC (FRAG. NO:1120) (SEQ ID NO:10498)  
5'-TGCCCTCCCTTCCCTCCTGG (FRAG. NO:1121) (SEQ ID NO:10499)  
20 5'-GGTGCCCTCCTTGGGCGCTGC (FRAG. NO:1122) (SEQ ID NO:10500)  
5'-GGTGCTCCTTGCCCC (FRAG. NO:1123) (SEQ ID NO:10501)  
5'-CTCTGGGTGGGCTGGC (FRAG. NO:1124) (SEQ ID NO:10502)  
5'-GGGGCGTCTCTGTGC (FRAG. NO:1125) (SEQ ID NO:10503)  
5'-CTGGCCTGGGTGCC (FRAG. NO:1126) (SEQ ID NO:10504)  
25 5'-GCCTCTCCTGGGGGGGTGGCTCCCTGTCC (FRAG. NO:1127) (SEQ ID NO:10505)  
5'-CCTTTTCCCCCGGCTCC (FRAG. NO:1128) (SEQ ID NO:10506)  
5'-GTGGGGGCTTTGGC (FRAG. NO:1129) (SEQ ID NO:10507)  
5'-GGG GGT CTG TGG CCT GCT CCT GGG G (FRAG. NO:1130) (SEQ ID NO:10508)  
5'-AGGGGTCTGGGGCCCTC (FRAG. NO:1131) (SEQ ID NO:10509)  
30 5'-TTTTTGGGGGTCTGGCTTG (FRAG. NO:1132) (SEQ ID NO:10510)  
5'-GCCTGGCTGCCTTCC (FRAG. NO:1133) (SEQ ID NO:10511)  
5'-GGGGCCTGCCGTGGGGC (FRAG. NO:1134) (SEQ ID NO:10512)  
5'-TGTCCTCTGTGTGCTCCCTT (FRAG. NO:1135) (SEQ ID NO:10513)  
5'-TGCTGTGTCTGG (FRAG. NO:1136) (SEQ ID NO:10514)  
35 5'-GGTTCCCGCCTTCCCT (FRAG. NO:1137) (SEQ ID NO:10515)  
5'-GTT CCC AGA GCT TGC CAC CTG CAG CAG GAC CAG GCA GCT CAC AGG GAA CAG GAG CCC AGA GCA AAG CCA CCC CAT  
TGG GAG ATG CCA AGG CAC CAG GCT G (FRAG. NO:1138) (SEQ ID NO:10516)  
5'-GTT CCC BGB GCT TGC CBC CTG CBG CBG GBC CBG GCB GCT CBC BGG GBB CBG GBG CCC BGB GCB BBG CCB CCC CBT  
TGG GAG BTG CCB BGG CBC CBG GCT G-3' (FRAG. NO:1139) (SEQ ID NO:10517)

5'-TCCCTGTTTC CCCCTTTTCG TTCTGCGTT GCCTTTGGCG TTTTGTGTT GTTTTCTCTC TCCGTTCTTC TTCTCCCTT  
GTGGGBBTTT CTGTGGGGBT GGCBTBCBG TBGGCBGCTC CBBGBCTBG CBBBCTCBBB TGCBBBGC BTTCTBTGGC  
TCTGBBBGCG TGGGAATTC TTGGGGBTG GCATACACGT CBBGAGCTCC AAGAGCTAGC AAACCTCAAAT GCAGAAGCATC  
CTCATCCCT TGAAGAAG-3' (FRAG. NO: 1759) (SEQ ID NO: 11141)

45 5'-GCC CCG GG-3' (FRAG. NO: 1760) (SEQ ID NO:11142)  
5'-G GGT TTC T-3' (FRAG. NO: 1761) (SEQ ID NO:11143)  
5'-GTG GGG BTG GC-3' (FRAG. NO: 1762) (SEQ ID NO:11144)  
5'-CCB BGB GCT BGC-3' (FRAG. NO: 1763) (SEQ ID NO:11145)  
5'-TCC CTG TTT CCC CCC TTT-3' (FRAG. NO:1140) (SEQ ID NO:10518)  
50 5'-CGT TCT GCG TTT GCC TTT GGC-3' (FRAG. NO:1141)(SEQ ID NO:10519)  
5'-GTT TTT TTG TTG TTT TCT-3' (FRAG. NO:1142)(SEQ ID NO:10520)  
5'-CTC TCC GTC TTT CTT CTC C-3' (FRAG. NO:1143) (SEQ ID NO:10521)  
5'-CCT CCT GCC TGT GTC CCT GCT CCC C-3' (FRAG. NO:1144) (SEQ ID NO:10522)  
5'-GAG GGT TCT TGG CTT CCT CTC T-3' (FRAG. NO:1145) (SEQ ID NO:10523)  
55 5'-TGT CTC TCT GTC CTT TTG TT-3' (FRAG. NO:1146) (SEQ ID NO:10524)  
5'-TGT TGT GCG GCC TGG TGC TGC CCT GCC CCG GG-3' (FRAG. NO:1147) (SEQ ID NO:10525)  
5'-GTG GGA ATT TCT GTG GGG BTG GCA TAC ACG TAG GCA GCT CCA AGA GCT AGC AAA CTC AAA TGC AGA AGC ATC CTC  
ATG GCT CTG AAA CG-3' (FRAG. NO: 1764) (SEQ ID NO:11146)  
5'-GTG GGB BTT TCT GTG GGG BTG GCB TBC BCG TBG GCB GCT CCB BGB GCT BGC BBB CTC BBB TGC BGB BGC BTC CTC  
60 BTG GCT CTC BBB CG-3' (FRAG. NO:1148) (SEQ ID NO:10526)

5'-CTCAGTGGCC CCAAAAAGGA TGAGTAATAC ATGCGCCACG ATGATCATAT CCTTTTACT ATGAGGCGGT GTCTGTCGTG  
TCTTTCTTTT GCTCTTGGTG TGCTTTTGCT GTGCCCTGCC TCCTCTGCCG TGCTGTGCT GTCTTTCTTT TGCTTTGGT  
GTGTCCTTGG TGCGCCCTGC CTCTCTGCC CGTGCTGTC GTGCTTTTCC TTGCTCTTG GTGTGCTTT GCTGTGCCCT

70 5'-CCG TGT C-3' (FRAG. NO: 1766) (SEQ ID NO:11148)  
5'-GCCCTGCC-3' (FRAG. NO: 1767) (SEQ ID NO:11149)  
5'-CCG TGT CTG TCG TGT CT-3' (FRAG. NO:1149) (SEQ ID NO:10527)  
5'-TTCCCTTTGCTCTTG-3' (FRAG. NO:1150) (SEQ ID NO:10528)  
5'-GTGTGTCCTTTGCTGT-3' (FRAG. NO:1151) (SEQ ID NO:10529)  
5'-GCCCTGCCTCTCTGC-3' (FRAG. NO:1152) (SEQ ID NO:10530)  
5'-CT CBGTGGCCCC CBBBGGGTG BGTBBTBCBT GCGCCBCBT GBTCBTBTCC TTTTBTCTBT GBGG (FRAG. NO: 1768) (SEQ ID NO:11150)

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### **Human IL-6 Nucleic Acid and Antisense Oligonucleotide Fragments**

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5'-CTCCTGGGGG TBCTGGGGCB GGGBBGGCBG CBGGCBBCBC CBGGBGCBG CCCBGGGBG BGGCBCTGG BCCGBBGGCG  
CTTGTGGGBG BGGBTCTBT BGCTGGGCTC CTGGGGGGG BGTBGGC-3' (FRAG. NO:1777) (SEQ ID NO:11159)

#### Human Monocyte-derived Neutrophil Chemotactic Factor

##### Nucleic Acid and Antisense Oligonucleotide Fragments

- 5'-GGGGTGGBBB GGTITGGBT BTGTCTTBT GCBCTGBCBT CTBBGTTCTT TBGCBCTCCT TGGCBBBCT GCBCTTCBC  
BCBGGCTGC BGGBTCTBGG BBGGCTGCCB BGBBGGCCB GGCCBGGTTG GBBGTCTGT TTBCBCBGG TGBGTGGTT  
CCTTCCGGGCTTGTGTCTC TGCTGTCTCT TGGTCTCTC CGGTGGTTTC TTCTGGCTC TTGTCTTCTC TCTTGG CCCT TGCG-3'  
(FRAG. NO:1778) (SEQ ID NO:11160)
- 5'-GGBGT BTG-3' (FRAG. NO:1779) (SEQ ID NO:11161)
- 10 5'-GCBCTGBCBT CT-3' (FRAG. NO:1780) (SEQ ID NO:11162)
- 5'-CCG GTG G-3' (FRAG. NO:1781) (SEQ ID NO:11163)
- 5'-GG CCC TTG GC-3' (FRAG. NO:1782) (SEQ ID NO:11164)
- 5'-GCT TGT GTG CTC TGC TGT CTC T-3' (FRAG. NO:1192) (SEQ ID NO:10570)
- 5'-TGG TTC CTT CCG GTG GTT TCT TCC TGG CTC TTG TCC T-3' (FRAG. NO:1193) (SEQ ID NO:10571)
- 15 5'-TTC TCT TGG CCC TTG GC-3' (FRAG. NO:1194) (SEQ ID NO:10572)
- 5'-GGGGTGGBBB GGTITGGBT BTGTCTTBT GCBCTGBCBT CTBBGTTCTT TBGCBCTCCT TGGCBBBCT GCBCTTCBC  
BCBGGC-3' (FRAG. NO:1783) (SEQ ID NO:11165)

##### Human Neutrophil Elastase (Medullasin) Nucleic Acid and Antisense Oligonucleotide Fragments

- 5'-GGGCTCCCGC CGCBGGGT TBTGGGCTCC CBGBCCBCC CGCBCCGCGC GBCGTTTBC BTTCGCCBCG CBGTGCGCGG  
20 CCBCTGBCB GBBGTTGGGC GCBCTCBGGG TGGCGCCGCB GBBGTGGCCT CCGCGCBGCT GCBGGGBCBC CBTGBBGGGC  
CBGCGTGGG GCGCGCTCG CCGGCCCGCC BCBTCTCCG BGGCCBGGC GGTGCCCCC BGCBCBBGG CCGCBGGGC  
BCBGGCGGG BGBCBGCGG GTCCGGCGCC BGGGTCTGT GTGGGCTGG GGTCCGGGG TCTCTGCCCT TCCGTGCTGG  
TGGGGTGGG GCTCCGGGG TCTCTGCCCT TCCGTGCCG GTGGGCGGC GCTCGCCGC CCCCCCTGC CCGGTGGGCT  
25 CCGCGCGGC GCGGGCTGC CGGCCCTCG TGGTCTCTG TGGCGGGTC CCGGTCCCGG GGTGGGGCG CGBGTGCGCG  
GCCBGGGTC-3' (FRAG. NO:1784) (SEQ ID NO:11166)
- 5'-GG TGG GGC-3' (FRAG. NO:1785) (SEQ ID NO:11167)
- 5'-G GGG CCG-3' (FRAG. NO:1786) (SEQ ID NO:11168)
- 5'-GGC CGG GTC CGG G-3' (FRAG. NO:1787) (SEQ ID NO:11169)
- 5'-TGG TGG GGC TGG GGC TCC GGG GTC TCT GCC CCT CCG TGC-3' (FRAG. NO:1195) (SEQ ID NO:10573)
- 30 5'-CGC GTG GGG CCG CGC TCG CCG GCC CCC C-3' (FRAG. NO:1196) (SEQ ID NO:10574)
- 5'-CCT GCC GGG TGG GCT CCC GCC GCG-3' (FRAG. NO:1197) (SEQ ID NO:10575)
- 5'-CGC CGG CCG GGC GGC CCC TC-3' (FRAG. NO:1198) (SEQ ID NO:10576)
- 5'-GTG GGT CCT GCT GGC CGG GTC CGG GTC CCG GGG GTG GGG-3' (FRAG. NO:1199) (SEQ ID NO:10577)
- 5'-CGC GCG TCG GCG GCC GCG GGT C-3' (FRAG. NO:1200) (SEQ ID NO:10578)
- 35 5'-GGGCTCCCGC CGCBGGGT TBTGGGCTCC CBGBCCBCC CGCBCCGCGC GBCGTTTBC BTTCGCCBCG CBGTGCGCGG  
CCBCTGBCB GBBGTTGGGC GCBCTCBGGG TGGCGCCGCB GBBGTGGCCT CCGCGCBGCT GCBGGGBCBC CBTGBBGGGC  
CBGCGTGGG GCGCGCTCG CCGGCCCGCC BCBTCTCCG BGGCCBGGC GGTGCCCCC BGCBCBBGG CCGCBGGGC  
BCBGGCGGG BGBCBGCGG GTCCGGCGCC BGGGTCTGT GTGGGCTGG GGTCCGGGG TCTCTGCCCT TCCGTGC-3'  
(FRAG. NO:1788) (SEQ ID NO:11170)

##### Human Neutrophil Oxidase Factor Nucleic Acid and Antisense Oligonucleotide Fragments

- 5'-CGGGBGTGGG GGTCTGGBC GGCCTGGBG GCBTCCBGGG CTCCCTCCB GTCTTCTTG TCCGCTGCCB GCBCCCTTC  
BTTCBGGG CTGTGGCTT CCBCCBGGG CBTGTTBGG TBGBBCTBG BGCGCGGCC TCCBCCBGG BCBTGTCTT  
TCTGTCCG TGCCTCTCTG GGGTTTTCG TCTGGGTGGG CTCTCTCTT GGGGCTGCTG CTGGGCTCTT CTTTTGT  
40 CTGGCTGTG GCTCTCTCTG GCGCTTCC TGGGTGTCT GTTTTGTG GCTCCBCCB GGGCBCTG-3' (FRAG. NO:1789) (SEQ  
ID NO:11171)
- 5'-CGGGBGTGGG GG-3' (FRAG. NO:1790) (SEQ ID NO:11172)
- 5'-GCCBGCBCCC-3' (FRAG. NO:1791) (SEQ ID NO:11173)
- 5'-C CBC CBG-3' (FRAG. NO:1792) (SEQ ID NO:11174)
- 5'-GGC CTC CBC CBG GGB CBT G-3' (FRAG. NO:1201) (SEQ ID NO:10579)
- 50 5'-GTC CTT CTT GTC CGC TGC C-3' (FRAG. NO:1202) (SEQ ID NO:10580)
- 5'-TCT CTG GGG TTT TCG GTC TGG GTG G-3' (FRAG. NO:1203) (SEQ ID NO:10581)
- 5'-GCT TTC CTC CTG GGG CTG CTG CTG-3' (FRAG. NO:1204) (SEQ ID NO:10582)
- 5'-GGC TCT TCT TTT TGT TTC TGG CCT GGT G-3' (FRAG. NO:1205) (SEQ ID NO:10583)
- 5'-CTC TCT CGT GCC CTT TCC-3' (FRAG. NO:1206) (SEQ ID NO:10584)
- 55 5'-CTT GGG TGT CTT GTT TTT GT-3' (FRAG. NO:1207) (SEQ ID NO:1216)
- 5'-GGC CTC CBC CBG GGB CBT G-3' (FRAG. NO:1208) (SEQ ID NO:10586)
- 5'-CGGGBGTGGG GGTCTGGBC GGCCTGGBG GCBTCCBGGG CTCCCTCCB GTCTTCTTG TCCGCTGCCB GCBCCCTTC  
BTTCBGGG CTGTGGCTT CCBCCBGGG CBTGTTBGG TBGBBCTBG BGCGCC-3' (FRAG. NO:1793) (SEQ ID NO:11175)

##### Human Cathepsin G Nucleic Acid and Antisense Oligonucleotide Fragments

- 5'-CCCTCCBCT CTGCTCTGBC CTGCTGGBCT CTGGBTCTGB BGBTBCGCCB TGTBGGGGCG GGBGTGGGGC CTGCTCTCC  
60 GGCCTCCGCT GBTCTCCCT GCCTCBGCC CBGTGGGTBG GBGBBGGCC BGCBBGGCB GGBGTGGCTG CBTCTTCTT  
GGTGGGGCT GCTCTCCCG CCTCGGTG TGTCTGGGT TTTCCCGTC TCTGGTCTG CTTCGGGGT CGT-3' (FRAG.  
NO:1794) (SEQ ID NO:11176)
- 5'-GBBGTBCGCC-3' (FRAG. NO:1795) (SEQ ID NO:11177)
- 65 5'-CBGCCCCBG-3' (FRAG. NO:1796) (SEQ ID NO:11178)
- 5'-TCC CGT CTC TGG-3' (FRAG. NO:1797) (SEQ ID NO:11179)
- 5'-GTG GGG CCT GCT CTC CCG GCC TCC G-3' (FRAG. NO:1209) (SEQ ID NO:10587)
- 5'-TGT GTT GCT GG GTG TTT TCC CGT CTC TGG-3' (FRAG. NO:1210) (SEQ ID NO:10588)
- 5'-TCT GCC TTC GGG GGT CGT-3' (FRAG. NO:1211) (SEQ ID NO:10589)
- 70 5'-CCCTCCBCT CTGCTCTGBC CTGCTGGBCT CTGGBTCTGB BGBTBCGCCB TGTBGGGGCG GGBGTGGGGC CTGCTCTCC  
GGCTCCGCT GBTCTCCCT GCCTCBGCC CBGTGGGTBG GBGBBGGCC BGCBBGGCB GGBGTGGCTG-3' (FRAG. NO:1798)  
(SEQ ID NO:11180)

##### Human Defensin 1 Nucleic Acid and Antisense Oligonucleotide Fragments

5'-CCGGGGCTGC BGCBBCTCB TCBGCTCTTG CCTGGBGTGG CTCBGCCTGG GCCTGCBGGG CCBCCBGGBG BBTGGCBGCB  
 BGGBTGGCBG GGGTCTCTBT GGCTGGGGTC BCBGBTCTC TBGCTBQCB GGGTGBCCBG BGBGGGC GGG TCC TCB TGG CTG  
 GGG GCC TGG GCC TGC BGG GCC GCT CTT GCC TGG BGT GGC TC GCC CBG BGT CTT CCC TGG T GCTCAGCCTC  
 5 CAAAGGAGCC AGCCTCTCCC CAGTTCCTGA AATCCTGAGT GTTGCTGCC AGTCGCCATG AGAACTTCCT ACCTTCTGCT  
 GTTTACTCTC TGCTTACTTT TGTCTGAGAT GGCTCAGGT GGTAACTTTC TCACAGGCCT TGGCCACAGA TCTGATCATT  
 ACAATTGCGT CAGCAGTGGA GGGCAATGTC TCTATTCTGC CTGCCCGATC TTTACCAAAA TTCAAGGCAC CTGTTACAGA  
 GGGGAAGGCCA AGTGCTGCAA GTGAGCTGGG AGTGACCAGA AGAAATGACG CAGAAAGTGAA ATGAACTTTT TATAAGCATT  
 CTTTAAATAA AGGAAAATTG CTTTGAAGT AT CTGCAAGTGT AAAAAGATTG TATATCTGCT GTTTGATGAA TGCAGCACCC  
 10 ACTAGCCACA TAGTGCTCGT GAGCACTTGC AATGCGGCTA GGGTGATTTC AATTAACCTA AAAGAGAACA GCCACAGGGA  
 GCATGTGGCT GCCATATTGG ATGGTGCTGC TTTGAGAACA AAATGAGAGA AATGAAGCCT CTAITTTACCT TGGTTGGCGG  
 AACACATTGA AGGGACTCTG TATTGATACC AGGCTTCAA CTTTGGGAAG TGTACTGGCC AACTTAAACA CATCCACAGG  
 AGAATGAAGA GGTTTGGGAA GGGACCAGAA ACCAGGCATT GAGGACAATG AGAAGAGTTT TTCAAAAGTG GAATTACTGC  
 AAAAAGTGGA AAAATAGCCT TTGGATGGAA GTTACTGATG AGACAATTTC CATCGGTGTG AAAGCCATCT TTCCAACAGA  
 15 GATCTGCAAC ATGAGAATGT ACTGTCTCCT AGGTAGGCA TGGCCTCTTG TATTAGTCCG CTCAGGCTAC CAGATTATC  
 GTTTAAACTG CTTTAACTG GACCAGGCAT TTTAAACAAC AGAAATTTAT TTCTCGCAG TCCTGGAGGC AGGAAGCTG  
 CGATCAAGGT GGAAGCAGGG TTGGCTTCTT CTCAGGTGTC TGTCTTGGC TGGTAGATGA CCGCCGCTC CTGGGTCTC  
 CACATGGTCT TTCTCTGTG TGTGTCTGTC CCAATCTCTT CTTATAAGGA TGCAAGTCTT ATGGATCAGA GCACACCCCA  
 ATGACCGTGT TTAACCTGAA TCACCTCTTT AAAGTTTCTC TCTCCAAATA CAATCACCTC CTGAGGCAT CTAGGGCTT  
 20 CGACACAGGA ATTCTTTTCC TAGGGGATTC AGTTCAGTCC AAAACGCCA CCAGTGGAGA CTTGCAACAT GCGGCGCTGC  
 TGGTCCCTCG CCAGGAATAT CACAGGCGAC TGTTCCTGT TGCATGGAAT AGAAGGCTAT TCCAGAGTAC TGTCTTATT  
 TATCAGATCT GGGATATCG GAGAAGGCCA AAATAAGTCT CAAAGTAGAA AAAAAGTAT GAAAGTTTGA GAGAGTAAAC  
 ATAATTTTCA CCCGATGTGA AACGATCCTA GATTTCAGCT GAAATAGTGA TGTGGGAAGT GAGGGGGCCG GGATTCAAGG  
 CAGAGGGAAC AGCGTAACCTG AAGGCATGGA AGGAGGGAAG TGTAGGCTGT GTTTGAAGAG TGGCAGCTGC TTCCACATTT  
 25 CTAAACACA GGATGTGATT TTGGGGTGTG TTGAGACAAG GCAGAAAAT TGTTTGGAAA AATAACTTGA ATTCCTGCA  
 CATTAAAT CTCTCAGCAG AAGAAAACCC CACTCAGAAC CCCACTGTTC ATTCTTGGC TTGTATTGG SCACAGCTGG  
 CATAGCCCCA GACTGAGTAA GCTCTTCA GACCTCATTT CATGAGTAGC CCAAAGATC AATCATGGGC CAATTTCTTG  
 GAAGAGAAGA CTCTCCGGTG TTTTGCAGTT ATTTGTTCTG CTTTCCGAG ATGTTCTCA ATCGTTGCA CTACAAGCA  
 TGAGTCTGAA GTGTTTGTGT TCCCTCTTA CAGGTGGTAA TTTCTCACA GGCCTTGGCC ACAGATCTGA TCATTACCA  
 30 TGGTTCAGCA GTGGAGGGCA ATGTCTCTAT TCTGCTTGC CGATCTTTAC CAAATTTCAA GGCACCTGTT ACAGAGGGAA  
 GGCCAAGTGC TGCAAGTAGC CTGAGAGTGA CCAAGAGAAA TGACGCAGAA GTGAAATGAA CTTTTATAA GCATTCTTT  
 AATAAAGGAA AATTGCTTTT GAAGTATACC TCCTTTGGC CAAATGAAAT CTTGTGTCTC AATTGGAAGA GTTAAAGAA  
 TAGGGGGTTA GGTGTCATGG GTTGAACGT GAGACAGGTC GAACCACAAA GCCTGCCTGG AAAAGGGGAG TGACGTCTA  
 GGCTTCAGTG ATGTGACCTC CACTTTGTTT GATCCACAAA CCAACAGGTG ACTGATTTTG GTCAGCTCAG CCTCCAAAGG  
 35 AGCCAGCCTC TCCCAAGTTC CTGAAATCCT GAGTGTGGC TGCCAGTCGC CATGAGAAT TCTACCTTC TCGTGTITAC  
 TCTCTGCTTA CTTTGTCTG AGATGGCCTC AGGTGGTAA TTTCTCACAG GCCTTGGCCA CAGATCTGAT CATTACAATT  
 GCGTCAGCAG TGGAGGGCAA TGTCTTATT CTGCTGCCC GATCTTTACC AAAATTTAAG GCACCTGTTA CAGAGGGGAG  
 GCCAAGTGCT GCAAGTGAGC TGGAGTGAC CAGAAGAAAT GACGCAGAAG TGAATGAAC TT -3' (FRAG.NO:1799) (SEQ ID  
 NO:12379)  
 5'-GTCAGCTCAG CCTCCAAAGG AGCCAGCCTC TCCCAAGTTC ATGAAATCCT GAGTGTGGC TGCCAGTCGC CATGAGAACT  
 40 TCCTACCTTC TGCTGTTTAC TCTCTGCTTA CTTTGTGCTC AGTGGCCTC AGGTGGTAA TTTCTCACG CCCTTGCCA  
 CAGATCTGAT CATTACAATT GCGTCAGCAG TGGAGGGCAA TGCTCTATT CTGCTGCCC GATCTTTACC AAAATTTAAG  
 GCACCTGTTA CAGAGGGGAG GCAAGTGCT GCAAGTGAGC TGGAGTGAC CAGAAGAAAT GACGCAGAAG TGAATGAAC TT-  
 3' (FRAG.NO: ) (SEQ ID NO:11844)  
 5'-CTGCAAGTGT AAAAAGATTG TATATCTGCT GTTTGATGAA TGCAGCACCC ACTAGCCACA TAGTGCTCGT GAGCACTTGC  
 45 AATGCGGCTA GGGTGATTTC AATTAACCTA AAAGAGAACA GCCACAGGGA GCATGTGGCT GCCATATTGG ATGGTGCTGC  
 TTTGAGAACA AAATGAGAGA AATGAAGCCT CTAITTTACCT TGGTTGGCGG AACACATTGA AGGGACTCTG TATTGATACC  
 AGGCTTCAA CTTTGGGAAG TGTACTGGCC AACTTAAACA CATCCACAGG AGAATGAAGA GGTTTGGGAA GGGACCAGAA  
 ACCAGGCATT GAGGACAATG AGAAGAGTTT TTCAAAAGTG GAATTACTGC AAAAAGTGGA AAAATAGCCT TTGGATGGAA  
 50 GTTACTGATG AGACAATTC CATCGGTGTG AAAGGCATCT TTCCAACAGA GATCTGCAAC ATGAGAATGT ATGTTCTCT  
 AGGTAGCGA TGGCCTCTTG TATTAGTCCG CTCAGGCTAC CAGATTATC GTTTAAACTG CCCATAACA GACCAGGCAG  
 TTTAAACAAC AGAAATTTAT TTCTCGCAG TCCTGGAGGC AGGAAGTCTG CGATCAAGGT GGAAGCAGGG TTGGCTTCTT  
 CTCAGGTGTC TGTCTTGGC TGGTAGATGA CCGCCGCTC CCGGGTCTT CACATGTGCT TTCTCTGTG TGTGTCTGTC  
 CCAATCTCTT CTTATAAGGA TGCAAGTCTT ATGGATCAGA GCACACCCA ATGACCGTGT TTAACCTGAA TCACCTCTTT  
 55 AAAATTTCTC TCTCCAAATA CAATCACCTC CTGAGGCATC GTTAGGGCTT CGACACAGGA ATTCTTTTCC TAGGGGATTC  
 AGTTCAGTCC AAAACGCCTA CCAGTGGAGA CTTGCAACAT GCGCGCCTGC TGGTCCCTCG CCAGGAATAT CACAGGCGAC  
 TGTTCCTGTG TGCATGGAAT AGAAGGCTAT TCCAGAGTAC TGTCTTATT TATCAGATCT GGGATACTGG GAGAAGGGCA  
 AAATAAAGTC CAAAGTAGAA AAAAAGTAT GAAAGTTTGA GAGAGTAACT ATAATTTCAG CCCGATGTGA AACGATCCTA  
 GATTTCAGCT GAAATAGTGA TGTGGGAAGT GAGGGGGCCG GGATTCAAGG CAGAGGGAAC AGCGTAACTG AAGGCATGGA  
 60 AGGAGGGAAG TGTAGGCTGT GTTTGAAGAG TGGCAGCTGC TTCCACATTT CTAAACACA GGATGTGATT TTGGGGTGTG  
 TTGAGACAAG GCAGAAAACCT TGTTTGGAAG AATAACTTGA ATTCCCTGCA CATTTAAAT CTCTCAGCAG AAGAAAACCC  
 CACTCAGAAC CCCACTGTTC ATTCTTGGC TTGTATTGG SCACAGCTGG CATAGCCCCA GACTGAGTAA GCTCTTCA  
 CACCTCATTT CATGAGTAGC CCAAAGATC AATCATGGGC CAATTTCTTG GAAGAGAAGA CTCTCCGGTG TTTTGCAGTT  
 65 ATTTGTTCTG CTTTCCGAG ATGTTCTCA ATCGTTGAG CTACAAGCCA TGAGTCTGAA GTGTTTGTGT TCCCTCTTA  
 CAGGTGGTAA CTTTCTCACA GGCCTTGGCC ACAGATCTGA TCATTACAAT TGCGTCAGCA GTGGAGGGCA ATGTTCTAT  
 TCTGCTGCC CGATCTTTAC CAAATTTCAA GGCACCTGTT ACAGAGGGAA GGCCAAGTGC TGCAAGTAGC CTGAGAGTGA  
 CCAGAAGAAA TGACGCAGAA GTGAAATGAA CTTTATAA GATTCTTTT AATAAAGGAA AATTGCTTTT GAAGTATACC  
 TCTTTGGGC CAAATGAAT CTTGTGTCTC AATTGGAAGA GTTAAAGAAG TAGGGGGTTA GGTGTCATGG GTTGAACGT  
 GAGACAGGTC GAACCACAAA GCCTGCCTGG AAAAGGGGAG TGACGTCTA GGCTTCAGTG ATGTACCTC CACTTTGTTT  
 70 GATCCACAAA CCAACAGGTG ACTGATTTG-3' (FRAG.NO: ) (SEQ ID NO:11843)  
 5'-GCTCAGCCTC CAAAGGAGCC AGCCTCTCCC CAGTTCCTGA AATCCTGAGT GTTGCTGCC AGTCGCCATG AGAACTTCTC  
 ACCTTCTGCT GTTACTCTC TGCTTACTTT TGTCTGAGAT GGCCTCAGGT GGTAACTTTC TCACAGGCCT TGGCCACAGA  
 TCTGATCATT ACAATTGCGT CAGCAGTGA GGGCAATGTC TCTATTCTGC CTGCCGATC TTTACCAAAA TTCAAGGCAC  
 CTGTTACAGA GGAAGGGCCA AGTGTGCAA GTGAGCTGG ATGTACCAGA AGAAATGACG CAGAAGTGAA ATGAACCTTT  
 75 TATAAGCATT CTTTAAATAA AGGAAAATTG CTTTGAAGT AT-3' (FRAG.NO: ) (SEQ ID NO:11841)  
 5'-CCGGGGC-3' (FRAG.NO:1800) (SEQ ID NO:11182)

5'-GG GCCTGCBGGG CC-3' (FRAG.NO:1801) (SEQ ID NO:11183)

5'-GGCBBGCB BGG-3' (FRAG.NO:1802) (SEQ ID NO:11184)

5'-GGG TCC TCB TGG CTG GGG-3' (FRAG. NO:1212) (SEQ ID NO:10590)

5'-GCC TGG GCC TGC BGG GCC-3' (FRAG. NO:1213) (SEQ ID NO:10591)

5'-GCT CTT GCC TGG BGT GGC TC-3' (FRAG. NO:1214) (SEQ ID NO:10592)

5'-GCC CBG BGT CTT CCC TGG T-3' (FRAG. NO:1215) (SEQ ID NO:10593)

5'-CCGGGGCTGC BGCBBCTCB TCBGCTCTTG CCTGGBTGG CTCBCCTGG GCCTGCBGGG CCBCCBGGBG BBTGGCBGCB  
BGGBTGGCB GGGTCTCTBT GGCTGGGGTC BCBGTCCTC TBGCTBGGCB GGTGBCCBG BGBGGGC-3' (FRAG.NO:1803)  
(SEQ ID NO:11185)

# 10 **Human Defensin 2 Nucelic Acid and Antisense Oligonucleotide Fragments**

5-ATCCTTTAA G TCAATGGACT TTGCATCAGT CACACCATCT TTTGTTACTT TGGACTTCCC CAGCTATGTT CAATAATTAC  
TGTTCTTCCC TTGGGCCCCA TTGTAATGGC TACAGCCTCG AAAAAAAGTC TACACTTTGA AGCATTAAAG CTCGGACATC  
AGCACCAAAT TTTACATCTT TACCATCACT TCAAGTGAGG TGAGGAGCCA GTAGCCTGGA CACTGGTCTC ATCTGGTGAA  
AGACTGTGGG TAATGGAAAGC ATTTCTGTGG GGTGCTGGCA GGACATGTGC ATGGCGAGGC AGGTCAATCA CAGCAAGTGA  
15 GAGCTGCCTC TTACTTTCTA AAGGTGACAT AGCAAATATA CAAAAAATAA TAAATAAATT ATTAATTTAG GTAGAGCACA  
TAAAGGCTTT ATTTCAATAT CCATTCTCT GTATGCTTTC TTCACCAGGA AGAAATAGTT TTAGTGTCAG GAATGAATGA  
GTCTGCCCCC GAATCCAGC CTGCTCAACA CACAAGGAAA CAAAGCCCTG ACAATCAGAG TGAATCCCTG GTGACTAAGC  
TCCCAGTCTT CGATGCATAT TTGTTTAGCA GTTCTGACAG CATTGACCC AGCCCTCTCT CTGCATATCC CATCAGAACC  
TCTTTTCTT TTTTCTTCT TGAGACTGAG TCTTGCTCTG TCGGAAGCGA CTCCTGTGCC TCAGCTCTCC AAATACCTGG  
20 AATTATAGGC GTAAGCCATC ATGCTGCTGCT AATTTTGTGA TTTTTCATGG AGATGGGGTT TTGCCATGTT GGTCAAATGG  
GTCTCACACT CCTGACCTCA TGTGATCCAC CTGCTCAGC CTCCCAAAT GCTGGGATGA CAGGTGTAAG CCACCATGCT  
AGGCTCAGAA ATTTCTTTT ATAAAAATGT CATTAAAGGAT CTGGCTGCA CAATATCGTT ACCAGCTTCC TTAAATCCA  
CTTCTGGCCT GCCAGGAATC AGGTCTCTCA GAACCTGACA TTTTAAATGA AGAGGTCAAG CAGTTCATGA GGAAGCCTC  
ATTGTCCTCA TGCTCTGTC ACTGCTGCAC CCCTGAGACA TCACAGACAT GGACACTGGG GCCTGCTTGT TTCTCAAAT  
25 GCCTTAGAT CGAAAGAGGG AGGAACCCAG ATGAATGCCA CTCATTTTCC CAAGAAAGGC CCTCTCTGCA GTGCCCGGGA  
TGGGGCTCTG TCCATTGCTT GGGGCCGCCA ATTGCTACTC TGGGTTACGG AGGAAGGACA GGGTCTGAG AGACACCAGA  
GAGCTCACAC AGCCTGAAA ACATGGGGCT CCTTCAATAG GTTTTCCCAT CACCAACAGG GAGACACAGT GGAGGCTTG  
CAGCCCACTC TGCTTTCTT CCACCAATC CCAAGGCCAG TGACCTGAC GTCTGTGGAA AGCAGAGAAA CCCCTGGCTC  
CCAAAGCCCT GAAGTCCCTG TGGAGCTGAC ATTCCTGAG TGACGGTGTG AATGGAAGGA ACTCAAGTGC GGGTGGTAGG  
30 CCACCTCTG GCCCAGGCTT GGGTGAACCT TGAGGGGACA CATGTAGTCA CAATCCCATC CTCCATCTT CTCTCTCAGA  
GGAAGGAAGT GGCATCCAT CTGCTCATC TCTTCCCGT GGGGAAGATG GGGAGTTTCA GGGGAATCTT CACATAAAT  
TCACCACTG AGATCTCTG TGAGGATGGG GCCCACCATG CTCCCGTGC TGCCAGAGGC CCTGAGCCCC TCCCAGGGTC  
CCTGGGTTG AGCCAGCCT GTATCATCCC CAGGAGCTGA ATGTCAAGC AATGGATAGA ATTAGATGGA AAGAGCTCTC  
AATTGACCT GAGACTGTCC CCAGATACTC AGGAAAAACA GGACGTGCA CAGAGTGGC AGCAGGTGAG TGGCAGGTTA  
35 TAGTCTCTGA GTTTGAGTT GTTCTACGT GAGACAGACC CAGCCCTCA CTCCATTCAC ACCTGGGTT TTAATGGTG  
CAAGATAGGA GCAATTTCTT GGTCCCAAGA GCAGGAGGAA GGGATTTCTT GGGGTTTCTT GAGTCCAGAT TTGCATAAGA  
TCTCTGAGT GTGCATTTGT CTTTGAGGAC CATTCTCTGA CTCACCAAGT AAGTGGCTGA ATTCTAACCT CTGTAATGAG  
CATTGCAACC AATACCAAGT CTGAAGCTCA CTTGGTGACC AGGGACCAAG ACCTTTATAA GGTGGAAGGC TTGATGTCTT  
CCCCAGACTC AGCTCCTGTT GAAGCTCCCA GCCATCAGCC ATGAGGGTCT TGTATCTCCT CTCTCTGTC CTCTTCATAT  
40 TCTGATGCC TCTTCCAGT GAGATGGGCC AGGGAATAG GAGGTTTGG CAAATGGAAG AATGGCGTAG AAGTCTCTG  
TCTGCTCTCA TTCCCTTCCA CCTATCTCT CCTCATCCCT CTCTCTCTG TGTGTCCCTT CATCTCTTTT  
CTCTGCTTC TCTCTCTCT TCCCTCTCT TCTTTTCTT GTCTTCTTT TTCTCTCTC CCTAGAGCAT GTCTTCTTT  
CTTCTCTTT CTCTTCTCT ACCCACACTT TTAGACTGAA TGCCCTATT AATTGAACAA AGCATTTGCT TCTCAATAG  
AAAAGGATT TGAGAACCCA ATGGACACT CACTGTTCT TCTAAGCCAA TATGAAGGAG CCCAGTAGCT TGTAAATATC  
45 ATCTCTTCA TGCTTTCCAT GCTACAACTG CTGAGACTAT GGTGAAACC TGTTAGGTGA CTTTTTAAAT AAAAGGCAGA  
AATTTTGATT TTATCTAAAG AAAGTAGTAT AGAATGTAT TTTCTAAAT TTTATATTTA AAGGGTAGAT ACTGCAACCT  
AGAGAATTCC AGATAATCTT AAGGCCAGC CTATAGTGT AGAAGTCA CAGCAAGACA CTCTGCCTCC AGGACTTTTC  
TGATCAGAGG CCTGAGAAC AGTCCCTGCC ACTAGGCCAC TGAAGGTTCA CAGGACAGGG TACAGCCCAT TGAACCTAC  
TTTTAAACCT GGATGCCTAA CCTTCATTTT CTCTTGATA TTATGAAAAT AAAATAAAAA CCATGAAAGG ATAAAAGAGG  
50 GAGAGTGGAA GGAAGGATG GAGAAAGGGA AAAAGAAAAT TTGAGAGTAA ATCTAAAAAC AATTAATCTA ATAGATATCA  
TCTGTGAAA TCCTCATTTT ACCAATCTTA TTTATGAGTC CTGGTTTGG TGAGAACAAT GGGGTCTGA GAGCACCAG  
AGACCTCATG TTTTCAAAA CCTAGAACAG TATAATGAAG GAAGGCGGGG AGGCAGGGAG GCAGGGAGGC AGGGAGGCAG  
GGAGGCGGGC AGGTGGGGAG GGAGGGACGG AAGGAGGGAG GGAGGGAGGG AGGGAGGGAG GGAGGGATAA AAAAAGAAGA  
ATGAGGTTGA AACCAGGACT TAGATATTAG AAACAAGCCA TTACAAAAT TATTCTATG GTTAATTGTG GTTTTCAACT  
55 GTAAGTTACT TGGTGTAAAT TTCCTATTAA ACAATTTTCA TAAGTTGCAT CTTTTATCC CATCTCAGGT CAAATACTTA  
ACAGACTAAA TGATTTGAAA AAGCAAAAGT TTAATGGCTT GTGTGTGTTA AAATGGAGGT ATGGTGGCTT TGATATTATC  
TCTTGTGGT GGAGCTGAAT TCACAAGAGA TCGTTGCTGA GCTCCTACCA GACCCACCT GGAGGCCCA GTCACTCAGG  
AGAGATCAGG GTCTTTCACA ATCAGGTTCT AAAAAAATAA ACATCCCCC AACCACAGCA GTGCCAGTTT CCATGTCAGA  
AATTAAGAT CAAATGACTG ACTCGCGTCT CATTATCATG ATGGAAGAGC CCAGGCTTGA GAAAGAAGCC CGCTGCGGAT  
60 TTAATCAAGG CGATAGTAC ACAGGTTTGG TGTTTTTCCA ACATGAGTTT TGAGTTCTTA CACGCTGTTT GCTCTTTTG  
TGTGTTTTT CCTGTGTTAG TGTTTTTGGT GGTATAGGCG ATCTGTATC CTGCCTTAA AGTGGAGCCA TATGTCATCC  
AGTCTTTTGC CTAGAAGGT ATAAACAAAT TGGCACCTGT GGTCTCCCTG GAACAAAATG CTGCAAAAAG CCATGAGGAG  
GCCAAGAAGC TGCTGTGGCT GATGCGGATT CAGAAAGGGC TCCCTCATCA GAGACGTGCG ACATGTAAAC CAAATTAAC  
TATGGTGTCC AAAGATACGC AATCTTTATC CTAGTAATTG TGGTCAATTG GTGATGTTGG TTTGGGACAG CCATCTCTAA  
65 TATCCTTGAA ACACCTTTT CTGCTCTCCA GGAAGGGGTC AGGGCTGCCA CAGCGGGGCT TGGAGTGCTT TCCAGGGTCA  
CAGGCACTGT TATTTCTTGG ATTCCTTGAC CTTCCTCATT TATTCCTGGC ATTTCTCTAA AACGTGTGCT TTGCTCTCC  
TGCATCTCC CCTTGCATGC CCTCACCTAC CCCACATCTT CCTTAAAAA AGCAAGCCCA ACTCAAAGAC CAGTTCCCTC  
ATGGAATCAT AGTGGATCTG CCAAGGGAGG GGATGCCCAG TCTCTGTTC TTCACAAGAC TCCCTTCTT TGGCTAAGGT  
TCTTATGCA ATAT GAATTCACAT TTCTCACTT TTGATGATT AAGAAAGTAT GGAGAAATAT ATCTCTATC AAATTTTCT  
70 GCCTTCAATA ATTTCTAAT CATCAGTAC TGTTTTTCCA TCTTTACTG TGATGATGCC CTCTCTTCCA AACTTTTCA  
TTGCATCAGA GATGATGTTA CCAATTTCTT TGTCTCCATT TGCAGAAATT GTAGCAACCT GTGCAATTTT TTCAGGTTTG  
GTACAGGTT TAGACTGCTT TTTAAGTTCA GCAATTCAG CATCAACAGC TAACATCACA CCTCTCTTGA TTTCACTGG  
ATTAGACCT TTGCTAACCT TCTGGAAGGC TTATTGGAA ATAGAGCATA CCAGTACAGC AGCAGTGATA GTGCCATCCC  
CCAGTCTCTC CATTGTGTTT ATTTGGCAACA TCTTGGACAA GTTTAGCTCC AATGCTTTTA TATTTATCCT TTAAGTCAAT  
75 TGACTTTGCA TCAGTCACAC CATCTTTTGT TACTTTGGGA CTTCCTCAGC TATGTTCAAT AATTACTGTT CTTCCTTTG

GCCCCATTGT AATGGCTACA GCATCGACAA AAAGTCTACA CTTTGAAGCA TTAAGGCTCA GACATCAGCA CCAAATTTTA  
 CATCTTTACC ATCACTTCAA GTGAGGTGAG GAGCCAGTAG CCTGGACACT GGTCTCATCT GGTGAAAGAC TGTGGGTAAT  
 GGAAGCATT CTGTGGGGTG GTGGCAGGAC ATGTGCATGG TGAGGCAGGT CATCAGCAGC AAGTGAGAGC TGCCCTCTAC  
 TTTCTAAAGT TGACATAGCA AGTATACAAA AAAAAATAAA ATATTAATTT AGGCAGAGCA CATAAAGGCT TTATTTTCATA  
 5 TTTCAATTTCT CTGTATGCTT TCTTCACCAG GAAGAAATAG TTTTAGTGTC AGGAATGAAT GAGTCTGCC CTCAATTTCCA  
 GCCTGCTCAG CACACAAGGA AACAAAGCCC TGACAATCAG AGTGACTCCC TGGTGACTAA GCTCCAGTCC TGGATGCATA  
 TTTGTTTAGC AGTCTTGACA GCATCTGACC CAGCCCTCTC TTTGCATACC CCACCAGAAC CTCTTTTTTT TTTTTTTTC  
 TTTGAGACTG AGTCTTGCTC TGTGGAAGC GATTCCCGTG CCTCAGCCTC CCAAATACCT GGAATTATAG GCGTAAAGCCA  
 10 TCATGCCTGG CTAATTTTTG TATTTTTTCAT GGAGATGGGG TTTTGCCATG TTGGTCAAAT TGGTCTCACA CTCCTGACCT  
 CATGTGATCC ACCTGCCTCA GCCTCCCAAA GTGCTGGGAT GACAGGTGTA AGCCACCATG CTAGGCTCAG AAATTTCTCT  
 TTATAAAAT GTCATTAAGG ATCTTGGCTG CACAATATCG TTACCAGCTT CCTTTAAATC CACCTCTGCG CTGCCAGGAA  
 TCAGGGTTCT TGAGAACCTG ACATTTTAAA TGAAGAGGTC AGGCAGGTCA TGAGGAAAGC CTCATGTGTC CCATGTCTCT  
 GTCATGCTG CACCCCTGAG ACATCACAGA CATGGACACT GGGGCTGCT TGTTCCTCAA ACTGCCCTTA GATCGAAAGA  
 15 GGGAGGAACC AGGATGAATG CCACTCATTT TCCCAAGAAA GGGCCTCTCC TGAGTGCCCG GGATGGGGCT CTGTCCATTG  
 CCTGGGGCCG CCAATTCCTA CTCTGGGTTA CGGAAGAAGG ACAGGGTCTT GAGAGACACC AGAGACCTCA CACAGCCCTG  
 AAAACATGGG GCTCCTTCAT AAGTGTTCCT CATCACCAAC AGGGAGACCA CGTGGAGGCC TTGCAGCCCT ACTCGGTGCT  
 TCTCCACCAA ATCCCAAGGG CAGTGACGCT GACGTCTGTG GAAAGCAGAG AAAGCCCTGG CTCCCAAAGC CCTGAAGTCC  
 TGTGAGACTG ACATTCCTGT AGTGACGGT TGAATGGAAG GAATCAAGT GCGGGTGGTA GGCCACCTCG TGGCCAGGCC  
 20 CTGGGTGAAC TCTGAGGGGA CACATGTAGT CACAATCCCA TCTCCCAT CTCTTCTCA GAGGAAGGAA GTGGGCATCC  
 ATCTGCCTCA TCTCTCTCCC GTGGGGAAGA TGGGGAGATT CAGGGGAATT TTCACATAAA TTTACCAGC TCAGACTCTCC  
 TGTGAGGATG GGGGCCACCA TGCTCCCGT GCTGCCAGAG CCCTGAGCC CTCTCAGGGT CCCTGGGTTT GAGCCAGGCC  
 TGTATCATCC CCAGGAGCTG AATGTCCGAA CAATGGATAG AATTAGATGG AAAGAGCTCT CAATTTGGCC TGAGACTGTC  
 CCCAGATACT CAGGAAAAC AGGACGTGCG ACAGAGTGGG CAGCAGGTGA GTGGCAGGTT ATAGGTCTGT AGTTTGAGTT  
 25 TGTCTCAGG TGAGACAGC CCAGCCCTC ACTCCATTCA CACACTGGGT TTTAAATGGT GCAAGATAGG AGGAATTTTC  
 TGGTCCCAAG AGCAGGAGGA AGGAGATTTT TGGGGTTTCC TGAGTCCAGA TTTGCATAAG ATCTCTGAG TGTGCATTGT  
 TCTTTGAGGA CCATTCTCTG ACTCACCAGG TAAGTGGCTG AATTCTAAC TCTGTAATGA GCATTGCACC CAATACCACT  
 TCTGAACCT ACCTGGTGAC CAGGGACCA GACCTTTATA AGGTGGAAG CTGTGATGTC TCCCAAGCT CAGCTCTGG  
 TGAAGCTCCC AGCCATCAGC CATGAGGGTC TTGTATCTCC TCTCTCGTT CCTCTTCATA TTCTGTATGC CTCTTCCAGG  
 TGAGATGGGC CAGGGAATA GGAGGGTTGG CCAAATGGAA GAATGCGGTA GAAGTCTCT GTCTCCTCTC ATTCCTCTCC  
 30 ACCTATCTCT CCCTCATCCC TCTCTCTCT TCTCTCTCT GTGTGTCCCC TCCATCTCTT TCTCTGCTT CTCTCTCTC  
 TTCCCTCTCT CTCTTTTTT CTGTCTTCT TTTTCTCTC TGTCTAGAGC ATGTCTTCT TTCTTCTCT TCTCTTCTT  
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- 5 5'-CCTACCTTGC TATAGAAGAC CTGGGACAGA GGACTGCTGT CTGCCCTCTC TGGTACCCT GCCTAGCTAG AGGATCTGTG  
ACCCAGCCA TGAGGACCTT CGCCATCCTT GCTGCCATTC TCCTGGTGGC CCTGCAGGCC CAGGCTGAGC CACTCCAGGC  
AAGAGCTGAT GAGGTGTGCTG CAGCCCCGGA GCAGATTGCA GCGGACATCC CAGAAGTGGT TGTITCCCTT GCATGGGACG  
AAAGCTTGGC TCCAAAGCAT CCAGGCTCAA GGAAAAACAT GGACTGCTAT TGCAGAATAC CAGCGTGCAT TGCAGGAGAA  
10 CGTCGCTATG GAACCTGCAT CTACCAGGGA AGACTCTGGG CATTCTGCTG CTGAGCTTGC AGAAAAAGAA AAATGAGCTC  
AAAATTTGCT TTGAGAGCTA CAGGGAATTG CTATTACTCC TGTACCTTCT GCTCAATTTC CTTT-3' (FRAG. NO: ) (SEQ ID  
NO:11847)
- 5'-GAATTCCTG TAAGCCCTGT TACAGGGGCT GCACCCAGTA TACAACCTGA CCTGTGTCCA AGGCGGGCAA CTCAACCCCTT  
AGATATTGAA TGGGTCCCAT GGCACCAATG CTAAACACCC AGCAGCCCTC ACAACCACAG ATCGTGTITT AAGGATGAGG  
15 AGGTAGTTCT CTGGATTGCAC AGGCTTACAT CCAAAATGGGC TCATGACGCC GCAGCACACA CCCAGTCTGC AGCCTGAAGA  
GTGGAGCAT TGCAATCACA GAAAGCATCC AGACATGATC ATGGGCTCAG GGATACACCT GTTCTCCGAT GTGTACCAAGT  
GAAGGATGGA AACTCCTATG CCTCCAGAA AGCACCCTC AAGCTTTTGC TGAATGCTTC TCTGAAGGCC CACAAGGCTG  
AGAGGCTGTG CAACACCAGC AGTAAAGTGA ATGCCAGAGC TCCACCTCC TTTCTTGGGT GGCCATCTGG AAAGGCCACT  
CCCACCTGA TGGTAATGC CTCAGACCAG TTCTTGGGCC AGATGATCCT AGACAATTGT TTAAGCTTAA ACTGTTTCAAT  
20 GGCCAGCAA ACAGGTGATA GTACCTCTGG GGAACCACAT GCCCGTGTA CATCCAGATC TCAGGAGAAC CCAAAAATGT  
CTGTTCACCA TAGCAACAGA AGCCCAAGTA GCACCTAGTC TCACCTGGGT GTTCTCCAAC ATCCCAAGCTC AGCCAAATGG  
CTTTCATTAG TTTTATGGT TAGACCCAG GTCTCGGGA CACTGCTTTA GAAACACATT CCAAATCCTC CTCTGTGTGC  
AGGTGGCATT CCTATCCCAA TCTCTTTGCA GGGCGTATAC TGTGATACGC AGCCAGGCTG TCCAGAGGCT CTTAAATATT  
CCCTTGGTGC AGGTAGITCA GCTTAGCCAC AGCCAATGCA TCACAGGCTC AACTGTGTTA GGAGCCATTG AGAATCCATA  
25 GTTGGTTGCT GCCTGGGCTT GGCCAGGGCT GACCAAGGTA GATGAGAGGT TCCTCTGTGG AGTTCTACTT TAACCTCACC  
TTCCACCAA ATTTCTCAAC TGTCTTGGC ACCACAATTA TTTAATGGAC CCAACAGAAA GTAACCCCGG AAATTAGGAC  
ACCTCATCCC AAAAGACCTT TAAATAGGGG AAGTCCACTT GTGCACGGCT GCTCCTTGGT ATAGAAGAC TGGGACAGAG  
GACTGCTGTC TGGCCTCTCT GGTACCCCTG CTTAGCTAGA GGATCTGTAA GTACTACAAA ACTTAACTT TACACTGAGT  
TTTCATCAAT GAAGCTATGC CTCCAATCTG ACCTCTGACT GTGGGGCCGC CCCAGAGGGA CCCAGCGGGT GAATCCCTGC  
30 TAGGAACGTC TGTCCGACC TCTGGTACT GCTGGGGACG ATGGCTTCCA GCTAACTTAA TAGAGAACT CAAGCAGTTT  
CCTCTAAAT ACACATGTC CATGTCTGG TTGACATGTC CAGTAAGAAAG ACTATCACAG GTCTTTGGAA CATCTTTTG  
AGAGAAACCT ATTTAGGTTC TTGGTCTGTT TTCAATCAG GTTGTGTTGAT TTTTGTATT GAGTTGTGG AATTCCCTAT  
GTATTCAGAT ATTTGCCCTT TCTGCCATGT AGGTTTGGCA AATATTTTCT CTCATTTTCT GGGTTATCTT TCACTCGGT  
TGATTGTTTC CTTGTGCTG CAGATGCTTT AGCGTTAAAT GAAGCCACAC TTGTCTATT TCCCTTTTAT TGCTGTGTC  
35 TTGGTGTCA TAGCCAAGAA ATCATTACCT ACATCAATGT CAAAAGCTTT ATCCTTCTAT ACATTCTAG TAGTTTATGG  
TTTCAGTTGT TACATTAGG TTTTCAATTC ATTCTGAGTT GATGTTCTTA CATGGTGTGA GATAAAGATT TAAATACATA  
CATATATAAA ATCATGAGGT AGTGTACACT ATAAATATAC AATTGTTAAT TGTACTCAA GTCTAAGTAG AGGTGGAAT  
AATAAACTTT CTTTTTTTTA CTAAACCAC TCTGTGTCAC TGAGCTGATT TCACCTTAG CCTGATAAAA TCATTGTCTT  
CTCCACCCTG ATTCCTACAG GAGACTACT ACCCCATAAC CTCAAAACCT TCCTCATGAG GATGGTAAGT CACCTGAATC  
40 CTGAAGTGA TTAAGTCTA TTCCATTGGA ACCTATATAG GACACCAGAA TCTAGACCTC CAGAGAACAG CAGGACCCAT  
CTTCAGAAAA TAAGAAGCAT TTGTCCCTG AGCCTGTTGA ATCAAAGTGC AATTCTTATT CTTTTTGGAA TGTAAAAAG  
TGAATCATAA TATTAAAGCA GGTGAACCCA CGAGTAACAT AGCAGGGTCT TTCTGTGCTAT TATTAGCTCC AACCTAGCAC  
AGACATAAAA GTGTACAGCA TATACTAGCA TGAACCTGGG AGAACAGGAG CATTGAGCA ACCTTGAGAC AACTGGCCCT  
CTCTTATAAA ATGCACACCT CCTCTCACTG AGATTGAGGA AGGTTTCTTG TCTCCGAGCC TTCTCCAGT AGAGCTATAA  
45 ATCCAGGCTG GCTCCTCCTT CCCCACACAG CTGCTCCTGC TCTCCTCCT CCAGGTGACC CCAGCCATGA GGACCTCGC  
CATCCTTGCT GCCATTCTC TGGTGGCCT GCAGGCCAG GCTGAGCCAC TCCAGGCAAG AGCTGATGAG GTTGTGTCAG  
CCCCGGAGCA GATTGACGCG GACATGCCAG AAGTGGTTGT TTCCCTGCA TGGGACGAAA GCTTGGCTCC AAAGCATCCA  
GGTGAGAGAG GCAGGCATGC AGAGCTGCTA AGTCTAGAGG GAAGGACGGG AGAGAGGTTT CAGAGTTGGG TCTCAGCAGT  
CTATGTCACT GAGGTGGCTT CACTTAGAAT CTCTGGGCTT TGATTTTCTC ATCTAGAAAT TGAACAGAGA GCCAAATAAA  
50 CTTGAGAAAT TTTATTTCTT CAAAGACTTG ATTTCAAGAA ACATCTGTGA AATTCACTAA GTTTAAGATA TGAAGAGACA  
GACTAGTTAT TTCTGGATCT AAACAAGTAG ACTTAGTTGT AAAGAGAACA TTTTACTCTA TCTACAGAAG AGCTTTTAAA  
AACTGCAGCC AAGCCTGAGG GTAAGTTTCA GTGTGTGTGT GATGGGGCAG GAATGCAAAA ATGAGAGCAA AGGAGAATGA  
GTCTCAAAT CTGTGTGACA AGCACTGCTC TGCCTGTGTTA TTCTATCGA CTGAGGTTGT TCGTGCTACC GGCTGCAATG  
CAGCCAGCAT CACCTGTGAG CTAGCATGTG ACTTCCCCGA GATTCTTTT CTTACCCACT GCTAACTCCA TACTCAATTT  
55 CTCTGTCTCT CCTGTCCCA GGCTCAAGGA AAAACATGGA CTGCTATTGC AGAATACCAG CGTGCAATGC AGGAGAACGT  
CGCTATGAAA CCTGCATCTA CCAGGGAAGA CTCTGGGCTT TCTGTGCTG AGCTTGCGA AAAAGAAAAA TGAGCTCAAA  
ATTTGCTTTG AGAGCTACAG GGAATTGCTA TTAATCTCTG ACCTTCTGCT CAATTTCTT TCTCATCTC AAATAAATGC  
CTTGTACAA GATTTCGTG TTCCACCTC TTAATGTGT GATATGTGTC TGTGTCAAGA CACTTGGGAT ACACGTACCA  
AAACGCAAAA TCAAAATTTT GAACAATATA-3' (FRAG. NO: ) (SEQ ID NO:11846)
- 60 5'-GGCBGCBGG-3' (FRAG. NO:1805) (SEQ ID NO:11187)  
5'-GG CTG GGG-3' (FRAG. NO:1806) (SEQ ID NO:11188)  
5'-GGGGTCBCC-3' (FRAG. NO:1807) (SEQ ID NO:11189)  
5'-GGG TCC TCB TGG CTG GGG TC-3' (FRAG. NO:1216) (SEQ ID NO:10594)  
5'-CCT CTC TCC CGT CCT-3' (FRAG. NO:1217) (SEQ ID NO:10595)
- 65 5'-CGTGCBBTC TGCTCCGGG CTGCBGCBBC CTCBTCBGCTC TTGCCTGGBGTG GCTCBGCTGG GCCTGCBGGG  
CCBCCBGGGB BTGGCBGCBG GBTGGCBGCG TCCTCBTGGC TGGGGTCBCT GGBGGBGGGB GBGCBGG-3' (FRAG.  
NO:1808) (SEQ ID NO:11190)

#### Human Macrophage Inflammatory Protein-1-alpha/RANTES

#### Receptor Nucleic Acid and Antisense Oligonucleotide Fragments

- 70 5'-GTCTTTGTTT CTGGGCTCGT GCCCBTCCC GGCTTCTCTC TGGTCCGTC CTCTGTGGTG TTTGGCCCTG CTTCCTTTTG  
CCTGTTGAGG GGGCAGCAGT TGGGCCCAA AGGCCCTCTC GTTCACCTTC TGGCAGGAGT GCATCCCCATA GTCAAACCTCT  
GTGGTCTGT CATAGTCTC TGTGGTGTG GGAGTTTCCA TCCCGGCTTC TCTCTGGTTC CAAGGGAGB GGGGGCBGCB  
GTTGGGCCCC BBBGGCCCTC TCGTTCBCT TCTGCBGCG BGTTGCBTCC CCBTBTGTCBB BCTCTGTGGT CGTGTCTBTG  
TCTCTGTGG TGTGTTGGBT TTCCBTCCCG GCTTCTCTCT GGTTCBBSGG GB-3' (FRAG. NO:1809) (SEQ ID NO:11191)

- 5'-GGGCC CC-3' (FRAG. NO:1810) (SEQ ID NO:11192)  
 5'-GGGGGCBGC-3' (FRAG. NO:1811) (SEQ ID NO:11193)  
 5'-CCCGGCTTC-3' (FRAG. NO:1812) (SEQ ID NO:11194)  
 5'-GTC TTT GTT TCT GGG CTC GTG CC-3' (FRAG. NO:1218) (SEQ ID NO:10596)  
 5'-CCB TCC CGG CTT CTC TCT GGT TCC-3' (FRAG. NO:1219) (SEQ ID NO:10597)  
 5'-GTC CTCTGT GGT GTT TGG-3' (FRAG. NO:1220) (SEQ ID NO:10598)  
 5'-CCC TGC TTC CTT TTG CCT GTT-3' (FRAG. NO:1221) (SEQ ID NO:10599)  
 5'-GAGGGGGCAG CAGTTGGGCC CCAAAGGCC TCTCGTTCAC CTCTGGCAC GGAGTTGCAT CCCCATAGTC AAACCTCTGTG  
 GTCGT-3' (FRAG. NO:1222) (SEQ ID NO:10600)  
 5'-GTCATAGTCCTCTGTGGTGTGGAGTTTCCATCCCGGCTTCTCTCTGGTTCCAAGGGA-3' (FRAG. NO:1223) (SEQ ID NO:10601)  
 5'-GBGGGGGCBG CBGTTGGGCC CBBBGGGCC TCTCGTTCBC CTCTGGCBC GGBGTTGCBT CCCCBTBGTC BBBCTCTGTG  
 GTCGTG-3' (FRAG. NO:1224) (SEQ ID NO:10602)  
 5'-TCBTBGTCTCTGTGGTGTGGBTTCBTTCCCGGCTTCTCTCTGGTTCCBBGGGB-3' (FRAG. NO:1225) (SEQ ID NO:10603)  
**RANTES Antisense Oligonucleotide Fragments**  
 5'-GGGCBGCGGG CBGTGGGCGG GCBTGTBGG CBBBGCBCB GGGTGTGGT TCCBGGBBT BTGGGGBGGC BGBTGCBGGB  
 GCGCBGCGG CBGTBGCBBT GBGGBTGBCB GCGBGGCGTG CCGCGGBGBC CTCTBTGGTB CCTGTGGBB GGCTGTGCGB  
 GGGGGTGTGG TGTCGCTTG GCGGTCTTT CCGGTGTTT TTCTCTGGGT TGGCCTGCTG CTCGTCGTGGT CGCTCCGCTC  
 CCGGTTCTGT CTCGCTCTG CGCCCTTCC TCCTTGTG TGTTCCTCC TTCCTGCT CT-3' (FRAG. NO: 1813) (SEQ ID  
 NO:11195)  
 5'-GGGTTGGC-3' (FRAG. NO: 1814) (SEQ ID NO:11196)  
 5'-CGGG CBG-3' (FRAG. NO: 1815) (SEQ ID NO:11197)  
 5'-CCCGGTTG-3' (FRAG. NO: 1816) (SEQ ID NO:11198)  
 5'-GGGTGTGGT-3' (FRAG. NO: 1817) (SEQ ID NO:11199)  
 5'-GGGCBGCGGG CBGTGGGCGG GCBTGTBGG CBBBGCBCB GGGTGTGGT TCCBGGBBT BTGGGGBGGC BGBTGCBGGB  
 GCGC-3' (FRAG. NO:1226) (SEQ ID NO:10604)  
 5'-BGBGGGCBGTB GCBTGBGGB TGBCBGCBG GCGTGCCGCG GGBBCCTCB TGTBCTGT GGBBGGCTG TCGBGG-3'  
 (FRAG. NO:1227) (SEQ ID NO:10605)  
 5'-GGGTGTGGTGTCCGCTTGGCGGTTCTTCGGGTGTTTCTCTCTGGGTGGCCTGCTGCTCGTCTGCTG-3' (FRAG. NO:1228) (SEQ  
 ID NO:10606)  
 5'-GCTCCGCTCCCGGTTCTGCTCTGCTGCCCCCTTCTCTCTGCTGTTCTCTCCCTTCTTGCCTCT-3' (FRAG. NO:1229)  
 (SEQ ID NO:10607)  
 5'-GGGTGTGGTGTCCG-3' (FRAG. NO:1230) (SEQ ID NO:10608)  
 5'-CTTGGCGGTTCTTTCGGGTG-3' (FRAG. NO:1231) (SEQ ID NO:10609)  
 5'-TTTCTCTCTGCGTTGCG-3' (FRAG. NO:1232) (SEQ ID NO:10610)  
 5'-CTGCTGCTCGTCTGTGTC-3' (FRAG. NO:1233) (SEQ ID NO:10611)  
 5'-GCTCCGCTCCCGGTTTC-3' (FRAG. NO:1234) (SEQ ID NO:10612)  
 5'-GTCTCGCTCTGTCGCCC-3' (FRAG. NO:1235) (SEQ ID NO:10613)  
 5'-CTTCTCTCTGTC-3' (FRAG. NO:1236) (SEQ ID NO:10614)  
 5'-GTGTTCTCTCCCTTCTTGCCTCT-3' (FRAG. NO:1237) (SEQ ID NO:10615)  
 5'-GGGCBGCGGG CBGTGGGCGG GCBTGTBGG CBBBGCBCB GGGTGTGGT TCCBGGBBT BTGGGGBGGC BGBTGCBGGB  
 GCGCBGCGG CBGTBGCBBT GBGGBTGBCB GCGBGGCGTG CCGCGGBGBC CTCTBTGGTB CCTGTGGBB GGCTGCGGB GG-3'  
 (FRAG. NO:1818) (SEQ ID NO:11200)  
**Human Muscarinic Acetylcholine Receptor HM1 Nucleic Acid and Antisense Oligonucleotide Fragments**  
 5'-GCTGCCCGG GGGGTGTGG CTGGCGCTC CCGTGCTCG TTCTGTCT CCCGGTCCCC CTGCTGGC GTCTCGGGCC  
 TTCTCTCT TCTCTTCTT CTTCCGCTC CGTGGGGGT GCTTGTGGG GGCCTGTGCT CCGGGTCCCG GGGCTTCTGG  
 CCCTTGGCGT TCAATGGTGGC TAGGTGGGG GTTCBTGGT GCTBGGTGG GC-3' (FRAG. NO:1819) (SEQ ID NO:11201)  
 5'-GGTGGGGC-3' (FRAG. NO:1820) (SEQ ID NO:11202)  
 5'-GCCCCGCGGG-3' (FRAG. NO:1821) (SEQ ID NO:11203)  
 5'-CGG GGC TTC TGG CCC-3' (FRAG. NO:1822) (SEQ ID NO:11204)  
 5'-GTT CBT GGT GGC TBG GTG GGG C-3' (FRAG. NO:1238) (SEQ ID NO:10616)  
 5'-GCT GCC CGG CGG GGT GTG CGC TTG GC-3' (FRAG. NO:1239) (SEQ ID NO:10617)  
 5'-GCT CCC GTG CTC GGT TCT CTG TCT CCC GGT-3' (FRAG. NO:1240) (SEQ ID NO:10618)  
 5'-CCC CCT TTG CCT GGC GTC TCG G-3' (FRAG. NO:1241) (SEQ ID NO:10619)  
 5'-GCC TTC GTC CTC TTC CTC TTC CTT CC-3' (FRAG. NO:1242) (SEQ ID NO:10620)  
 5'-GCT CCG TGG GGG CTG CTT GGT GGG GGC CTG TGC CTC GGG GTC C-3' (FRAG. NO:1243) (SEQ ID NO:10621)  
 5'-CGG GGC TTC TGG CCC TTG CC-3' (FRAG. NO:1244) (SEQ ID NO:10622)  
 5'-GTT CAT GGT GGC TAG GTG GGG C-3' (FRAG. NO: 1245) (SEQ ID NO:10623)  
**Human Muscarinic Acetylcholine Receptor HM3 Nucleic Acid and Antisense Oligonucleotide Fragments**  
 5'-GGG GTG GGT BGG CCG TGT CTG GGGGT GGC CBT GTT GGT TGC CTCT TGG TGG TGC GCC GGG CGCG TCT TGG CTT TCT  
 TCT CCT TCG GGC CCT CGG GCC GGT GCT TGT GGGCT CCT CCC GGG CGG CCT CCC CGG GCG GGG GCT TCT TGCGC CTG  
 GCG GGG GGG CCT CTGCT CTG TGG CTG GGC GTT CCT TGG TGT TCT GGG TGGTGG CGG GCG TGG TGG CCT CTG TGGGG  
 CCC GCG GCT GCB GGG GTTG CCT GTC TGC TTC GTCCCT TGC GCT CCC GGG CCG CCGGG GTG GGT AGG CCG TGT CTG  
 GGGGT GGC CAT GTT GGT TGC CCGG CCC GCG GCT GCA GGG G-3' (FRAG. NO:1823) (SEQ ID NO:11205)  
 5'-CCC GGG CGG-3' (FRAG. NO:1824) (SEQ ID NO:11206)  
 5'-G GCG GGG GGG CC-3' (FRAG. NO:1825) (SEQ ID NO:11207)  
 5'-CCC GGG CCG CC-3' (FRAG. NO: 1826) (SEQ ID NO:11208)  
 5'-GG CCG TGT-3' (FRAG. NO:1827) (SEQ ID NO:11209)  
 5'-GGG GTG GGT BGG CCG TGT CTG GGG-3' (FRAG. NO:1246) (SEQ ID NO:10624)  
 5'-GTT GGC CBT GTT GGT TGC C-3' (FRAG. NO:1247) (SEQ ID NO:10625)  
 5'-TCT TGG TGG TGC GCC GGG C-3' (FRAG. NO:1248) (SEQ ID NO:10626)  
 5'-GCG TCT TGG CTT TCT TCT CTT TCG GGC CCT CGG GCC GGT GCT TGT GG-3' (FRAG. NO:1249) (SEQ ID NO:10627)  
 5'-GCT CCT CCC GGG CGG CCT CCC CGG GCG GGG GCT TCT TG-3' (FRAG. NO:1250) (SEQ ID NO:10628)  
 5'-GCG CTG GCG GGG GGG CCT CCT CC-3' (FRAG. NO:1251) (SEQ ID NO:10629)  
 5'-GCT CTG TGG CTG GGC GTT CCT TGG TGT TCT GGG TGG C-3' (FRAG. NO:1252) (SEQ ID NO:10630)

5'-TGG CGG GCG TGG TGG CCT CTG TGG TGG-3' (FRAG. NO:1253) (SEQ ID NO:10631)  
 5'-GGG CCC GCG GCT GCB GGG G-3' (FRAG. NO:1254) (SEQ ID NO:10632)  
 5'-TTG CCT GTC TGC TTC GTC-3' (FRAG. NO:1255) (SEQ ID NO:10633)  
 5'-CTT TGC GCT CCC GGG CCG CC-3' (FRAG. NO:1256) (SEQ ID NO:10634)  
 5'-GGG GTG GGT AGG CCG TGT CTG GGG-3' (FRAG. NO:1257) (SEQ ID NO:10635)  
 5'-GTT GGC CAT GTT GGT TGC C-3' (FRAG. NO:1258) (SEQ ID NO:10636)  
 5'-GGG CCC GCG GCT GCA GGG G-3' (FRAG. NO:1259) (SEQ ID NO:10637)

#### **Human Fibronectin Antisense Oligonucleotide Fragments**

5'-CGG TTT CCT TTG CGG TC TTG GCC CGG GCT CCG GGT G CCC GCC CGC CCG CCG GCC GCC GC CCC GCC GGG CTG TCC  
 10 CCG CCC CGC CCC GGC CCG GGG CGC GGG GG CGG CCC TCC CGC CCC TCT GG GCC GGC GCG GGC GTC GG CCG CTC GCG  
 CCT GGG GTT CCC TCT CCT CCC CCT GTG C GCC TGC CTC TTG CTC TTCTGC GTC CGC TGC CTT CTC CC CTC TCC TCG GCC  
 GTT GCC TGT GC TGT CCG TCC TGT CGC CCT TCC GTG GTG C TGT TGT CTC TTC TGC CCT C GGT GTG CTG GTG CTG GTG  
 GTG GTG CCT CTG CCC GTG CTC GCCCTG CCT GGG CTG GCC TCT TCG GGT GTG GCT TTG GGG CTC TCT TGG TTG CCC TTT  
 CTT CTC GTG GTG CCT CTC CTC CCT GGC TTG GTC GT TGT CTG GGG TGG TGC TCC TCT CCC TTT CCC TGC TGG CCG TTT GT  
 15 CCT GTT TTC TGT CTT CCT CT TTC CTC CTG TTT CTC CGT TTG GCT TGC TGC TTG CCG GGC TGT CTC C CTT GCC CCT GTG  
 GGC TTT CCC TGG TCC GGT CTT CTC CTT GGG GGT C GCC CTT CTT GGT GGG CTGGCT CGT CTG TCT TTT TCC TTC C TGG  
 GGG TGG CCG TTG TGG GCG GTG TGG TCC GCC T TGC CTC TGC TGG TCT TTC-3' (FRAG. NO:1828) (SEQ ID NO:11210)  
 5'-GGCCCGGGC-3' (FRAG. NO:1829) (SEQ ID NO:11211)  
 5'-GCCGGCGCGGGCG-3' (FRAG. NO:1830) (SEQ ID NO:11212)  
 20 5'-GCCTGGGCTGGCC-3' (FRAG. NO:1831) (SEQ ID NO:11213)  
 5'-GGGGG TGGCCG-3' (FRAG. NO:1832) (SEQ ID NO:11214)  
 5'-GG GGG TGG CCG TTG TGG GCG G-3' (FRAG. NO:1833) (SEQ ID NO:11215)  
 5'-CGG TTT CCT TTG CGG TC-3' (FRAG. NO:1260)(SEQ ID NO:10638)  
 5'-TTG GCC CGG GCT CCG GGT G-3' (FRAG. NO:1261)(SEQ ID NO:10639)  
 25 5'-CCC GCC CGC CCG CCG GCC GCC GC-3' (FRAG. NO:1262)(SEQ ID NO:10640)  
 5'-CCC GCC GGG CTG TCC CCG CCC CGC CCC-3' (FRAG. NO:1263)(SEQ ID NO:10641)  
 5'-GGC CCG GGG CGC GGG GG-3' (FRAG. NO:1264)(SEQ ID NO:10642)  
 5'-CGG CCC TCC CGC CCC TCT GG-3' (FRAG. NO:1265)(SEQ ID NO:10643)  
 5'-GCC GGC GCG GGC GTC GG-3' (FRAG. NO:1266)(SEQ ID NO:10644)  
 30 5'-CCG CTC GCG CCT GGG GTT CCC TCT CCT CCC CCT GTG C-3' (FRAG. NO:1267)(SEQ ID NO:10645)  
 5'-GCC TGC CTC TTG CTC TTC-3' (FRAG. NO:1268)(SEQ ID NO:10646)  
 5'-TGC CTC CGC TGC CTT CTC CC-3' (FRAG. NO:1269)(SEQ ID NO:10647)  
 5'-CTC TCC TCG GCC GTT GCC TGT GC-3' (FRAG. NO:1270)(SEQ ID NO:10648)  
 5'-TGT CCG TCC TGT CGC CCT TCC GTG GTG C-3' (FRAG. NO:1271)(SEQ ID NO:10649)  
 35 5'-TGT TGT CTC TTC TGC CCT C-3' (FRAG. NO:1272)(SEQ ID NO:10650)  
 5'-GGT GTG CTG GTG CTG GTG GTG GTG-3' (FRAG. NO:1273)(SEQ ID NO:10651)  
 5'-CCT CTG CCC GTG CTC GCC-3' (FRAG. NO:1274)(SEQ ID NO:10652)  
 5'-CTG CCT GCG CCG TCT TCG GGT-3' (FRAG. NO:1275)(SEQ ID NO:10653)  
 5'-GTG GCT TTG GGG CTC TCT TGG TTG CCC TTT-3' (FRAG. NO:1276)(SEQ ID NO:10654)  
 40 5'-CTT CTC GTG GTG CCT CTC CTC CCT GGC TTG GTC GT-3' (FRAG. NO:1277)(SEQ ID NO:10655)  
 5'-TGT CTG GGG TGG TGC TCC TCT CCC-3' (FRAG. NO:1278)(SEQ ID NO:10656)  
 5'-TTT CCC TGC TGG CCG TTT GT-3' (FRAG. NO:1279)(SEQ ID NO:10657)  
 5'-CCT GTT TTC TGT CTT CCT CT-3' (FRAG. NO:1280)(SEQ ID NO:10658)  
 5'-TTC CTC CTG TTT CTC CGT-3' (FRAG. NO:1281)(SEQ ID NO:10659)  
 45 5'-TTG GCT TGC TGC TTG CCG GGC TGT CTC C-3' (FRAG. NO:1282)(SEQ ID NO:10660)  
 5'-CTT GCC CCT GTG GGC TTT CCC-3' (FRAG. NO:1283)(SEQ ID NO:10661)  
 5'-TGG TCC GGT CTT CTC CTT GGG GGT C-3' (FRAG. NO:1284)(SEQ ID NO:10662)  
 5'-GCC CTT CTT GGT GGG CTG-3' (FRAG. NO:1285)(SEQ ID NO:10663)  
 5'-GCT CGT CTG TCT TTT TCC TTC C-3' (FRAG. NO:1286)(SEQ ID NO:10664)  
 50 5'-TGG GGG TGG CCG TTG TGG GCG GTG TGG TCC GCC T-3' (FRAG. NO:1287)(SEQ ID NO:10665)  
 5'-TGC CTC TGC TGG TCT TTC-3' (FRAG. NO:1288)(SEQ ID NO:10666)

#### **Human Interleukin-1 (IL-1) Nucleic Acid and antisense Oligonucleotide Fragments**

5'-AAGCTTCTAC CCTAGTCTGG TGCTACACTT ACATTGCTTA CATCCAAGTG TGTTATTTC TGTGGCTCCT GTTATAACTA  
 TTATAGCACC AGGTCTATGA CCAGGAGAAT TAGACTGGCA TTAATCAGA ATAAGAGATT TTGCACCTGC AATAGACCTT  
 55 ATGACACCTA ACCAACCCCA TTATTACAA TTAACAGGA ACAGAGGGAA TACTTTATCC AACTCACACA AGCTGTTTTT  
 CTCCAGATC CATGCTTTTT TGCGTTTATT ATTTTITAGA GATGGGGGCT TCACTATGTT GCCACACTG GACTAAAACT  
 CTGGGCCTCA AGTGATTGTC CTGCTCAGC CTCCTGAATA GCTGGGACTA CAGGGGCATG CCATCACACC TAGTTCATT  
 CCTCTATTA AAATATACAT GGCTTAACT CCAACTGGGA ACCCAAACA TTCATTGCT AAGAGTCTGG TGTCTACCA  
 CCTGAAGTAG GCTGGCCACA GGAATTATAA AAGCTGAGAA ATTCTTAAT AATAGTAACC AGGCAACATC ATTGAAGGCT  
 60 CATATGTAAA AATCCATGCC TTCCTTTCTC CCAATCTCCA TTCCAAACT TAGCCACTGG TTCTGGCTGA GGCCTTACGC  
 ATACCTCCCG GGGCTTGCAC ACACCTTCT CTACAGAAGA CACACCTTGG GCATATCCTA CAGAAGACCA GGCTTCTC  
 TGGTCCITGG TAGAGGGCTA CTTTACTGTA ACAGGGCCAG GGTGGAGAGT TCTCTCTGA AGCTCCATCC CCTCTATAGG  
 AAATGTGTG ACAATATCA GAAGAGTAAG AGGATCAAGA CTTCTTTGTG CTCAAATACC ACTGTCTCT TCTTACCCT  
 GCCCTAACCA GGAGCTTGTC ACCCCAACT CTGAGGTGAT TTATGCCTTA ATCAAGCAA CTTCCCTCT CAGAAAAGAT  
 65 GGCTCATTTT CCCTCAAAAG TTGCCAGGAG CTGCCAAGTA TTCTGCCAAT TCACCCTGGA GCACAATCAA CAAATTCAGC  
 CAGAACACAA CTACAGTACT TATTAGAACT ATTATTATTA ATAAATTCCT CTCCAAATCT AGCCCTTGA CTTCCGATT  
 CACGATTCT CTCTCTCTCC TAGAAACITG ATAAGTTTCC CGCGCTTCCC TTTTCTAAG ACTACATGTT TGTCACTTA  
 TAAAGCAAAG GGGTGAATAA ATGAACCAA TCAATAACTT CTGGAATATC TGCAAAACAA AATAATATCA GCTATGCCAT  
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 70 TTGACGACGC ACTGTAGCC ACGTAGCCAC GCCTACTTAA GACAATTACA AAAGGCGAAG AAGACTGACT CAGGCTTAAG  
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 45 **Human Interleukin-1 Receptor (IL-1 R) Nucleic Acids and Anti-sense Oligonucleotide Fragments**  
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 GGGCCAGGA CGGTGCTCTG TGGCTTCTGC CAGCCTTGCA GGAGGACTCT GGCACCTACG TCTGCACTAC TAGAAATGCT  
 20 TCTTACTGTG ACAAATATGC CATTGAGCTC AGATGTTTGG AGAATACAGA TGCTTTCTCTG CCGTTCATCT CATACCCGCA  
 AATTTAACT TTGTCAACCT CTGGGTATT AGATGCGCT GACCTGAGTG AATTCACCCG TGACAAAAC GACGTGAAGA  
 TTCAATGGTA CAAGGATTCT CTCTTTTGG ATAAAGACAA TGAGAAATTT CTAAGTGTGA GGGGGACCAC TCACCTACTC  
 GTACACGATG TGGCCCTGGA AGATGCTGGC TATTACCGCT GTGTCTGAC ATTTGCCCAT GAAGGCCAGC AATACAACAT  
 CACTAGGAGT ATTGAGCTAC GCATCAAGAA AAAAAAAGAA GAGACCATTG CTGTGATCAT TTCCCCCTC AAGACCATAT  
 25 CAGCTTCTCT GTGGTCAAGA CTGACAATCC CGTGTAAAGGT GTTCTTGGGA ACCGGCACAC CCTTAACCAC CATGCTGTGG  
 TGGACGGCCA ATGACACCCA CATAGAGAGC GCCTACCCGG GAGGCCGGT GACCGAGGGG CCACGCCAGG AATATTCAGA  
 AAAAATAGAG AACTACATTG AAGTGCCATT GATTTTGTAT CCTGTACAAA GAGAGGATTT GCACATGGAT TTTAAATGTG  
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 CTGGCCCCAC TTTCACCTGC CTCTTGTGTT TTGGGGGAAA TATGATGCA CAGACGGTGC AAACACAGAA CTGGAAGAAG  
 30 AGATGGTCTG ACTGTGCTAT GGCCTCATCA TCAAGACTTT CAATCCTATC CCAAGTGAAA TAAATGGAAT GAAATAATTC  
 AAACACAAAA AAAAAAAAAA AAAAAAAA-3' (FRAG. NO.:)(SEQ ID NO:11887)  
 5'-GCCGGAGCCG ACTCGGAGCG CGCGGCGCGG CCGGAGGAGG CCGAGCGCGC GTGGGGGCGC CGGCTGCCCC  
 GCGCGCCAG GGAGCGCAG GAATGTGACA ATCGCGCGCC CGCACCGTAG CACTCTCGC TCGGCTCCTA GGGCTCTCGC  
 CCTCTGAGCT GAGCGGGTT CCGCCCGGC TGGGATCCA TCACCCTCA CGGCCGTCCG TCCAGGTAGA CGCACCTCT  
 35 GAAGATGGTG ATCCCTCTCT GAGAAGCTGG ACCCTTGGT AAAAGACAAG GCCTTCTCCA AGAAGAATAT GAAAGTGTTA  
 CAGACACTA TTGTTTATC AGCTTACTG ATTTCTTCT TGAGGCTGA TAAATGCAAG GAACGTGAAG AAAAAATAAT  
 TTTAGTGCA TCTGCAAAATG AAATTGATGT TCGTCCCTGT CCTCTTAACC CAAATGAACA CAAAGGCACT ATAATTGGT  
 ATAAAGATGA CAGCAAGACA CCTGTATCTA CAGAACAAGC CTCCAGGATT CATCAACACA AAGAGAACT TTGGTTTGT  
 CCTGCTAAGG TGGAGGATT AGGACATTAC TATTGCGTGG TAAGAAATTC ATCTTACTGC CTCAGAATTA AAATAAGTGC  
 40 AAAATTTTGG GAGAAATGAGC TAACTATTG TTATAATGCA AAGCCATAT TTAAGCAGAA ACTACCCGTT CGAGGAGACG  
 GAGGACTTGT GTGCCCTTAT ATGGAGTTTT TAAAAATGA AAATAATGAG TTACCTAAAT TACAGTGGTA TAAGGATTGC  
 AAACCTCTAC TTCTTGACAA TATACACTTT AGTGAAGTCA AAGATAGGCT CATCGTATG AATGTGGCTG AAAAGCATAG  
 AGGGAACATC ACTTGTACAT CATCTACAC ATACTTGGG AAGCAATATC CTATTACCCG GGTAATAGAA TTTATTACTC  
 TAGAGGAAAA ACCTACCAAG AGGCCTGTGA TTGTGAGCCC AGTCAATGAG ACAATGGAAG TAGACTTGGG ATCCAGATA  
 45 CAATTGATCT GTAATGTCAC CGGCCAGTTG AGTGACATTG CTTACTGGAA GTGGAATGGG TCAGTAATTG ATGAAGATGA  
 CCCAGTGCTA GGGGAAGACT ATTACAGTGT GGAAAAATCCT GCAAAACAAA GAAGGAGTAC CCTCATCACA GTGCTTAATA  
 TATCGGAAAT TGAAGTAGA TTTTATAAAC ATCCATTAC TGTTTTGGC AAGAATACAC ATGGTATAGA TGCAGCATAT  
 ATCCAGTTAA TATATCCAGT CACTAATTTT CAGAAGCACA TGATTGGTAT ATGTGTCACG TTGACAGTCA TAATTGTGTG  
 TTCTGTTTTC ATCTATAAAA TCTCAAGAT TGACATTGTG CTTTGGTACA GGGATTCCCT CTATGATTTT CTCCCAATAA  
 50 AAGCTTCAGA TGGAAAGACC TATGACGCAT ATATACTGTA TCCAAAGACT GTTGGGGAAG GGTCTACCTC TGACTGTGAT  
 ATTTTGTGTG TAAAGTCTT GCCTGAGGTC TTGGAATAAC AGTGTGATA TAAGCTGTTT ATTTATGAAA GGGATGACTA  
 CGTTGGGGAA GACATTGTTG AGGTCATTAA TGAAAACGTA AAGAAAAGCA GAAGACTGAT TATCATTTTA GTCAGAGAAA  
 CATCAGGCTT CAGCTGGCTG GGTGGTTCAT CTGAAGAGCA AATAGCCATG TATAATGCTC TTGTTCAAGG TGAATTTAAA  
 GTTGTCTCTG TTGAGCTGGA GAAAAATCCAA GACTATGAGA AATAGCCAGA ATCGATTAAA TTCATTAAGC AGAAACATGG  
 55 GGCTATCCGC TGGTCAGGGG ACTTTACACA GGGACCACAG TCTGCAAGA CAAGGTTCTG GAAGAATGTC AGGTACCACA  
 TGCCAGTCCA GCGACGGTCA CCTTCATCTA AACACCAGTT ACTGTCACCA GCCACTAAGG AGAACTGCA AAGAGAGGCT  
 CACGTGCCCT TCGGGTAGCA TGGAGAAGTT GCCAAGAGTT CTTTAGGTGC CTCCTGTCTT ATGGCGTTGC AGGCCAGGTT  
 ATGCCTCATG CTGACTTGCA GAGTTCATGG AATGTAACATA TATCATCCTT TATCCCTGAG GTCCACAGGA ATCAGG-3' (FRAG.  
 NO.:)(SEQ ID NO:11888)  
 60 **Human Interleukin-8 Fragments Antisense Oligonucleotide Fragments**  
 5'-GBTGTTTGT BCCBBBGBCT CBBGBBTBGC TTTGCTBTCT BBGBBTBCTB TTBGBCBTB GBBBBCGCT GTBGGTGBBB  
 BGBTGTGCTT BCCTTCBCBC BGBCTGCBG BBBTBGBBGG BTGCTCBGBGBG CCBGCGCCBGC TTGBGTCTBT GTTTCBCBCB  
 BTGBGGTGC TCCGGTGGCT TTTGCTTGT GTGCTCTGCT GTCTCTG TTC CTTCGGGTGG TTTCTTCTG GCTCTTGTCC  
 TTTCTCTGG CCCTTGGCCC-3' (FRAG. NO:1834) (SEQ ID NO:11216)  
 65 5'-G CTC CGG-3' (FRAG. NO:1835) (SEQ ID NO:11217)  
 5'-CBBBGBBTBGC-3' (FRAG. NO:1836) (SEQ ID NO:11218)  
 5'-CBCBC BTGBGGTGC-3' (FRAG. NO:1837) (SEQ ID NO:11219)  
 5'-BCCBBBGBCT CBBGBBTBGC-3' (FRAG. NO:1838) (SEQ ID NO:11220)  
 5'-GCCBBBGBGB CCBGCGCCBGC-3' (FRAG. NO:1839) (SEQ ID NO:11221)  
 70 5'-GTG CTC CGG TGG CTT TTT-3' (FRAG. NO:1289)(SEQ ID NO:10667)  
 5'-GCT TGT GTG CTC TGC TGT CTG TG-3' (FRAG. NO:1290)(SEQ ID NO:10668)  
 5'-TTC CTT CCG GTG GTT TCT TCC TGG CTC TTG TCC T-3' (FRAG. NO:1291)(SEQ ID NO:10669)  
 5'-TTC TCT TGG CCC TTG GCC C-3' (FRAG. NO:1292)(SEQ ID NO:10670)

5'-GBTGTTTGT BCCBBBGBCT CBBGBBTBGC TTTGCTBTCT BBGBBTBCB TTBGBCBTB GBBBBBCGCT GTBGGTCBGBB  
BGBTGTCCT BCCTTBCBC BGBGCTGCBG BBGTGGBBGG CTGCCBGBGBG CCBGCGCCBGC TTGGBGTCTB GTTTBCBCBC  
BGTGGBGTGC TCCGGTGCT TTTGCTTGT-3' (FRAG. NO:1840) (SEQ ID NO:11222)

**Human IL-8 Receptor Alpha Antisense Oligonucleotide Fragments**

- 5 5'-ACAGGGGCTG TAATCTTCATC TGCAGGTGGC ATGCCAGTGA AATTAGATC ATCAAAATCC CACATCTGTG GATCTGTAAT  
ATTTGACATG TCCTCTTCAG TTTAGCAAT GGTGTTGATCT AACTGAAGCA CCGGCCAGGB CBGGGGCTGT BBTCTTCBTC  
TGCBGGTGGC BTGCCBGTGB BBTBTBGTG BTBCCBBTCC CBCBTCTGTG GBTCTGTBBT BTTTGBCBTG TCCTCTTCBG  
TTTCBGCBB TGGTTTGTG TBBCTGBBG BCCGGCCBGG TGGCTCGGTG CTCTGCCCC TGTGTTGTGCG GCGCTCGGTT  
GGTGTGGCCC CTGTGTTGCT TCGTTTCCCC CTCTTCTCT TGTTCGCGG GTTCTTGTGG CCGGCTGCTT GTCTCGTTCC-
- 10 3'(FRAG.NO:1841)(SEQ ID NO:11223)  
5'-CBGGGGC-3' (FRAG. NO:1842) (SEQ ID NO:11224)  
5'-GCBGGTGGC-3' (FRAG. NO:1843) (SEQ ID NO:11225)  
5'-GCGGGCGCTC-3' (FRAG. NO:1844) (SEQ ID NO:11226)  
5'-TGGCTCGGTGCTTCTGCCCC (FRAG. NO:1293)(SEQ ID NO:10671)
- 15 5'-TGTGTTGCGGCGCTC (FRAG. NO:1294)(SEQ ID NO:10672)  
5'-GGTTGTTGTTGGCCCTG (FRAG. NO:1295)(SEQ ID NO:10673)  
5'-TGGTGCTTCGTTTCC (FRAG. NO:1296)(SEQ ID NO:10674)  
5'-CCCTCTTCTCTTGTTC (FRAG. NO:1297)(SEQ ID NO:10675)  
5'-GGGGTCTTGTGGC (FRAG. NO:1298)(SEQ ID NO:10676)
- 20 5'-GGGCTGCTGTCTCGTTCC (FRAG. NO:1299)(SEQ ID NO:10677)  
5'-ACAGGGGCTG TAATCTTCATC TGCAGGTGGC ATGCCAGTGA AATTAGATC ATCAAAATCC CACATCTGTG GATCTGTAAT  
ATTTGACATG TCCTCTTCAG TTTAGCAAT GGTGTTGATCT AACTGAAGCA CCGGCCAGG-3' (FRAG. NO:1845) (SEQ ID NO:11227)  
5'-B CBGGGGCTGT BBTCTTCBTC TGCBGGTGGC BTGCCBGTGB BBTBTBGTG BTBCCBBTCC CBCBTCTGTG GBTCTGTBBT  
BTTTGBCBTG TCCTCTTCBG TTTCBGCB TGGTTTGTG TBBCTGBBG BCCGGCCBGG-3' (FRAG. NO:1846) (SEQ ID NO:11228)
- 25 Interleukin-11 (IL-11) Nucleic Acid and Antisense Oligonucleotide Fragments  
5'-GCTCAGGGCA CATGCCCTCC CTCCCCAGC CGCGGCCAG CTGACCCCTCG GGGCTCCCC GGCAGCGGAC AGGGAAGGGT  
TAAAGGCCCC CGGCTCCCTG CCCCCTGCCC TGGGGAACCC CTGGCCCTGT GGGGACATGA ACTGTGTTTG CCGCTGTGTC  
CTGGTCTGTG TGAGCTGTG GCCAGATACA GCTGTGCGCC CTGGGCCACC ACCTGGCCCC CCTCGAGTTT CCCCAGACCC  
TCGGGCCGAG CTGGACAGCA CCGTGCTCT GACCCGCTCT CTCTCGCGG ACACGCGGCA GCTGTGCTGA CACGAGGGG  
30 ACAAATTCCT AGCTGACGGG GACCACAACC TGGATTCCCT GCCCACCTG GCCATGAGTG CCGGGGCACT GGGAGCTCTA  
CAGCTCCAG GTGTGCTGAC AAGGCTGCGA GCGGACCTAC TGTCTACCT GCGGCACGTG CAGTGGCTGC GCCGGCAGG  
TGGCTCTTCC CTGAAGACCC TGGAGCCCGA GCTGGGCACC CTGAGGCCG GACTGGACCG GCTGTGCGC CGGTGTCAGC  
TCCTGTATGC CCGCTGGCC CTGCCCCAGC CACCCCGGA CCGCGCGCG CCCCCGCTG CCCCCCTC CTCAGCCTGG  
GGGGGCATCA GGGCCGCCA CGCATCCTG GGGGGCTGC ACCTGACACT TGACTGGGCC GTGAGGGGAC TGCTGTGCT  
35 GAAGACTCGG CTGTGACCCG GGGCCCAAAG CCACACCGT CTTCCAAAG CCAGATCTTA TTATTATT TATTTCAGTA  
CTGGGGGCA AACAGCCAGG TGATCCCCC GCCATTATCT CCCCCTAGT AGAGACAGTC CTTCCGTGAG GCCTGGGGGA  
CATCTGTGCT TTATTATAT TTATTATTT CAGGAGGAG GGTGGGAGG AGGTGGACTC CTGGGTCCCC GAGGAGGAGG  
GGACTGGGT CCGGATTCT TGGGTCTCCA AGAAGTCTGT CCACAGACTT CTGCCCTGGC TCTTCCCAT CTAGGCCTGG  
GCAGGAACAT ATATTATTA TTAAAGCAAT TACTTTTCAT GTTGGGTGG GGACGGAGG GAAAGGGAAAG CCTGGGTTT  
40 TGTACAAAAA GTGAGAAAC CTTTGTGAGA CAGAGAACAG GGAATTAAT GTGTCATACA TATCC CAGTCCGGC  
ATCTCTGTG TCAGAGTCTT GTGTCTCTG TTCTTCCC CTGGGGTCT CCCTGGGTCT CCCCAGATCC CTCTGCTGT  
CTTCTCCCG CTCTCTGATC TCTGACTCCC AGAACCCTCT CCTCTGTCT CAGGGCTGCC CCTCTGATCC TCTTGTCTC  
TCTGGTGTG CTCTCTGGCT GCCTCCATCT CTGTGATCT CCGTCTCCCT GTCTCTGTCT CAGTCTGTCC TCACTCTGT  
TGTGTGTGT CTCTCTCTCT TCTCTCTCC TCCCTTCCA CTCCCTCTC CTCTGCTCC CACCTCTCA GGGCCCTGTC  
45 GTTCCCTCC GTCCGCCTT TCTCTGCCCT TCCGTCTCC TGCTTCCCA TCTCTCTG CTAGTCTGT CCAGCCGAG  
CCCCACCCAC AGTCGGGCC CAGCGCTGA GCCTGAGTGT CTGCTCGGC CCGTGGAGGT GGAGGGAGGG GACGCCAATG  
ACCTCACCAG CCCCTCTCCG ACCACCCCCC CTTTCCCTT TTCAACTTTT CCAACTTTT CTTCCGTGCC CTCTCCGAG  
CGCGCGCGG TGAGCCCTG AAGCGAGCCG CTCGCTCTGA ATGAAAAGG CAGGCAGGGA GGGTGAAGTCA GGATGTGTC  
50 GGCCGGCCCT CCCCTGCCG CTGCCCCCG CCGGCCCGC CAGGCCCCC TATATAACCC CCCAGGCGTC CACACTCCCT  
CACTGCCGCG GCGCCTGCTG CTCAGGGCAC ATGCTCCCT TCCCCAGCG CCGGCCAGC TGACCTCGG GGCTCCCCG  
GCAGCGGACA GGAAGGGTT AAAGGCCCCC GGCTCCCTG CCGCTGCCCT GGGGAACCC TGGCCCTGT GGGACATGAA  
CTGTAAGTGT GTTACATGG AGGTGGAGG GAGAGGAGG CAGGAGGGA CCGCGGGGT CCGGAGGAGG  
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55 CCGCGAGAGG AGCGAGACG GAGACCGAGC AGGGGAGG ACAGGAGGAC TGGTGCCGG AGGGAGGTGA CCCCATCGA  
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60 CGAGCTCCG ACCCCCGCG CCGCGGCC CCGCGCGCC CCGCGCGCA GCTCTCCG TCCCGCGCC CGGCCGGCC  
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65 AGCCCGCTG GCGCTGCGC CTGCCCGCG GCGTTCAC CTGGGACTTA AGACCTCCAG CTCCATCCT CCTAAGGCG  
GGAGTCCAG CCCCAGACCT TCCTCCCCA GACCCAGGAG TCCAGACCC AGGCCTTCT CCTCAGACC TAGGAGTCA  
GCCGCCAGC CTCTCTCC TCAGACCCAG GAGGACGAGT CACCCAGT CAGACCCG AGTCCAGCC  
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70 GGCCGAGCTG GACAGACCC TGCTCTGAC CCGCTCTCT CTGCGGAGA CCGGCAGCT GGCTGCACAG CTGTTAGGAG  
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ACCCTGCCA TGAGTGCAGG GGCAGTGGG GCTCTAGGAG TAAGGCAAG GAGTGGGCT GGGGAGCAAG TGGGAGGCA  
75 GCAGTGAAGG GGGCGGGGAG GATGAGGGG ACTGGTCGG TGTCTCTGA TGTCCCGCT CTATCCAG CTCCAGGTG

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 5 GCTCTGAGAC CCTGACCCTA ACAGTCTGTC TCTGAGACCC TGACCTTGCA GTCCCAAGAT CCTGTGGCCC TGAGACCCCTG  
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 AGTCCCCAGA TCCCAGCCCC TAAGACCCAA GACCCCAATC TGAAGCCCAA AGCCTTGAGA ATTCAAATCC TCACCTCAAG  
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 10 CTAAAAATAC AAAATTAGCC AGGCGTGGTG GTGCATGCCT GTAATCCAG CTACTTGGGA GGCTGAGGCA GGAGAATCGC  
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 TCTCTCTCAA AAAAAAAAAA AAAAAAAAAA AAGAAGGAAA AGAAAACCAT GGACCTCCAG ACCCTGAGAC CCCAGGCCCC  
 AGCCTCTAGA TCTTGACATC TTAAGATCC CAGGCCCTAA GATACAAGAC CTTGACCCAA AGCCAGCCTT GGGACCCCTG  
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 15 CACCTCAGAT CCTGAGCCTG CGCCTGTACG ACTCCAAGAC CCTCACTTCC AAAGCCAGGC CCAAAGCCCT GAGACCAGAA  
 GACTTCAAAC CCTGTTCTT GGGCCTAACT CCAAAGACCC TGGATCTCAA ATTCCAACCT CTAGCTCTGA GACTCCAGCC  
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 ACTCGAGCCC ACAGACCTCA GATACTGTCT GTAAAAACCC AGCTCTGGTG GGGAGCAGTG GCTCACTCCT GTAATCCCAA  
 GGCAGGGGAG GCCAAGGCAG AAGGACCTCT TGAGGCCATG AGTTTGAGAC AGCCTGGGCA GCATAGCAAG ACTCTGTTTC  
 20 TTAATTATTA TTATTATAT TATTTTTTGG AGACAGAGTC TCGCGCTCTG TTGCCAGGC TAGAGTGCAA TGGTGCCATT  
 TCGGCTTGCT GGAACCTCCG CCTCCTGGGC TCAAGCGATT CTCGCTGCTC AGCCTCCTGA GTAGTGCTC CTTCAGGTG  
 ACACCTGCCAC ACCCGGATAA TTTTTTGTG TTTTAGTAGA CACAGGGTTT CACCGTGTG CCCAGGCTGG TCACAACTC  
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 25 CTCACCTAGA ACAGAGATG CAGCCCTGAC TCCACAGACT TCAACCTGAA CCCCCACACT CAGCTCTGCA AGCCCTCTCT  
 GACTCCAGCC TCCATTTTCG GAACCCACA GCCTGAAGAG CTCCCGGCT AAACACTTCA CCCCACGCG CACAGTCCCC  
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 TCACTCTCT CCTCTCCCCA CAGATGTCCC GCCTGGCCCT GCCCCAGCCA CCCCCGACC CGCCGGCGCC CCCGCTGGCG  
 30 CCCCCTCTCT CAGCCTGGG GGGCATCAGG GCGGCCACG CCATCCTGGG GGGGCTGCAC CTGACACTTG ACTGGGCCGT  
 GAGGGGACTG CTGCTGCTGA AGACTCGGCT GTGACCCGGG GCCCAAAGCC ACCACCGTCC TTCCAAAGCC AGATCTTATT  
 TATTTATTTA TTTCAGTACT GGGGCGGAAA CAGCCAGGTG ATCCCCCGC CATTATCTCC CCTAGTTAG AGACAGTCT  
 TCCGTGAGGC CTGGGGGGCA TCTGTGCTT ATTTATACT ATTTATTCA GGAGCAGGGG TGGGAGGCAG GTGGACTCT  
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 35 TTCCCCATCT AGGCTGGGC AGGAACATAT ATTATTTATT TAAGCAATTA CTTTTCATGT TGGGGTGGG ACGGAGGGGA  
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 45 TCAGGGAGGC TAAGGAGAGA GGCTTGCTTG GGATATAGAA AGATATCCTG ACATTGGCCA GGCATGGTG CTCACGCTG  
 TAATCCTGGC ACTTTGGGAG GACGAAGCGA GTGGATCACT GAAGTCCAAG AGTTTGAGAC CGGCTGCGA GACATGGCAA  
 AACCTGTCT CAAAAAGAA AGAATGATGT CCGTCAATGA AACAGCAGG TACAAAACCA CTGCATGCTG TGATCCCAAT  
 TTTGTGTTT TCTTCTATA TATGGATTAA AAAAAAATC CTAAGGGGAA ATACGCCAAA ATGTTGACAA TGTATGTCTC  
 CAGGTCAAAG GAGAGAGGTG GGATTGTGGG TGACTTTTAA TGTGTATGAT TGTCTGTATT TTACAGAATT TCTGCCATGA  
 50 CTGTGTATTT TGATGACAC ATTTTAAAAA TAATAAACAC TATTTTAGA ATAACAGAAT ATCAGCTCC TCTCTCCAA  
 AAATAAGCCC TCAGGAGGGG ACAAAGTTGA CCGTGAATG AGCCTGTGAC GGCTGTGCAC-3' (FRAG. NO.:11892)  
 5'-GCTCAGGGCA CATGCTCTCC CTTCCAGGC CGCGGCCAG CTGACCCTCG GGGTCTCCCC GGCAGCGGAG AGGGAAGGGT  
 TAAAGGCCCC CGGCTCCTG CCCCCTGCC TGGGGAACCC CTGGCCCTGT GGGGACATGA ACTGTGTTTG CCGCCTGGTC  
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 55 TCGGGCCGAG CTGGACAGCA CGTGCTCCT GACCCGCTCT CTCTGGCGG ACACGCGGCA GCTGGCTGCA CAGCTGAGGG  
 ACAAATTCCT AGCTGACGGG GACCACAACC TGGATTCCCT GCCACCCCTG GCCATGAGTG CGGGGGCACT GGGAGCTCTA  
 CAGCTCCAG GTGTGCTGAC AAGGCTGCGA GCGGACCTAC TGTCTACCT GCGGCACGTG CAGTGGCTGC GCGGGCAGG  
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 60 TCCTGATGTC CCGCTGGCC CTGCCCCAGC CACCCCGGA CCGCGCGCG CCCCCTGTG CGCCCTCTG GGTAGGGGAC TGCTGTGCT  
 GGGGGCATCA GGGCCGCCA CGCCATCTG GGGGGGCTGC ACCTGACACT TGAAGGGGAC GTGAGGGGAC TGCTGTGCT  
 GAAGACTCGG CTGTGACCCG GGGGCCAAAG CCACCAACCT CCTTCCAAAG CCAGATCTTA TTTATTTATT TATTTAGTA  
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 CATCTGTGCC TTTATTTATC TTTATTTATC CAGGAGAGG GGTGGGAGGC AGGTGGACTC CTGGGTCCCC GAGGAGGAGG  
 GGAAGGGGT CCGGATTCT TGGGTCTCCA AGAAGTCTGT CCACAGACT CTGCCCTGGC TCTTCCCAT CTAGGCTGG  
 65 GCAGGAACAT ATATTATTTA TTTAAGCAAT TACTTTTCAT GTTGGGGTGG GGACGGAGGG GAAAGGGAAG CCTGGGTTTT  
 TGTACAAAAA TGTAGAAAC CTTGTGAGA CAGAGAACAG GGAATTAAAT GTGTCATACA TATCC-3' (FRAG. NO.:11890)  
 5'-CAGCTGCGG ATCCTCTGTC TCAGAGTCTT GGTGTCTCTG TTCCTTCC CTCGGGTCT CCTGGGTCT CCCCAGTCC  
 CTCTGCTGT CTCTCTCCG CTCTCTGATC TCTGACTCC AGAAGCTCTC CTCTGTCTC CAGGGCTGCC CACTGTATCC  
 70 TCTTGTCTC TCTGTGTGT CTCTCTGCT CTCTCCATCT CTGTGGATCT CCGTCTCCCT GTCTGTCTC CTCTGTCTC  
 TTCACTCTGT GTGTGTGTGT GTCTCTCTCT CTCTCTCTC TTCCTTCCA CTCCCTCTC CTCTGTCTC CACCTCTCCA  
 GGCCCTGTG TTGTCCCTC GTCCGGCCTT TCTCTGCTT TCCGTCTCTG TGCCCTCCCA TCTCTCTCTG CTAGTCTGT  
 CCAGCCGAG CCCCACCCAC AGTCGGGCC CAGCGCTTGA GCGTGAAGTC CTGCTCCGCG CCGTGGAGGT GAGGAGGAGG  
 CAGGCCAATG ACCTCAACAG CCCCCTCTCG ACCACCCGCC CTTTCCCTT TCAACTTTT CCAACTTTT CTCCGTGCGC  
 75 CTCTCTCGAG CGCGCGCGG TGAGCCCTGC AAGGCAGCCG CTCCGTCTGA ATGGAAGAG CAGGCAGGGA GGGTGAGTCA

GGATGTGTCA GGCCGGCCCT CCCCTGCCGC CTGCCCCCG CCCGCCGCC CCAGGCCCCC TATATAACCC CCCAGGCGTC  
 CACACTCCCT CACTGCCGCG GGCCTGCTG CTCAGGGCAC ATGCCTCCCC TCCCCAGCCG CGGGCCAGC TGACCTCTCG  
 GGCTCCCCCG GCAGCGGACA GGGGAAGGTTT AAAGGCCCCC GGCTCCCTGC CCCCTGCCCT GGGGAACCCC TGGCCCTGTG  
 5 GGGACATGAA CTGTAAGTTG GTTCATGGGG AGGGTGGAGG GGACAGGGAG GCAGGGAGGA GAGGGACCCA CGGCGGGGGT  
 GGGAGCAGAC CCCGCTGAGT CGCACAGAGA GGGACCCGGA GACAGGCAGC CGGGGAGGAG AGCAGCTTCG GAGACAGGAG  
 GCGGCGGAGG AGATGGGCAG AGAGAGACAC AGACAGGAGC GGATGGAGGC AGCCAATCAG AGGCGCCGCA GGAGGGACGG  
 GCCAGACAGG GCCCGAGAGG AGCGAGACGC GAGACGAGC AGGCGGAGG ACOCAGGGAG TGGTGCCGGG AGGGAGGTGA  
 CCCCCATCGA CCCAGGCCCC AGGGAGCCCG CGGGGACCGG GAGACTCCCT GGGATTCCGG CAGAGAGGCT CCGGAGGGAA  
 ACTGAGGCAG GGTCCGCGGA GAGCGAGCA AGCCAGGGAG TAGCGACCCC AGCCGGGGGG AGGAGAGAGA CTGGGCGCCG  
 10 GGGGAAAGCG GGGAGAGCCG GGCAGATGCG GCCGACGGAG GCGCGGACAG ACCGACGGCT GCGGGGCCG GGGGCGGGG  
 TGGGGGTGTG CGAGGCGCGG GCGGCGGGG AGCGCTGATT GGCTGGCGGG TGGCCGGGTG GCGGGGGCGG CCGGGGTGGG  
 CTGCGGGGAG CGAGCTCCGG ACCCCGCGCG CCCCGGCGCC CCCCGCGCCC CCCCGGCCA GCTCTCCCGC TCCCGGCGCC  
 CGGCGGGGAG ATGGCTCTGC CCTCTCCGC CCAGTGTGCG TGCGGCCCGG GCTTCTGCCG CCCACCCGCG GGGCTCTGTG  
 GAGGGCGTCT AAGGGGTCTC CCGTGGGAGA GGTCCGTGTC TCCCGGACTC CGTCTGGGC TTTTGGCTCC TTCCCTGTCT  
 15 CCCAGCCAGC TCGGGCTCCC GCGGCGGGG GAGGGGGCAG GTTCTGGCCT GTGCTCCCC CACCATCCGC GCGCGGGG  
 CCAGATTCCG GCGTCCGGGG GCGGACGGGA GACGCCCGGG CCGCGTCTGC TCCGACGGGC GGGGACAGCA GAGCCAGGGA  
 GGGAGAGGGA AGCCCGCCTG GCCCTGCGAC CTGCCCGCGG GCGTTCACCC CTGGGACTTA AGACCTCCAG CTCCATCTCT  
 CCTAAGGCGG GAGATCCAGG CCCCAGACCC TCCAGAGGAG TCCAGAGCCC AGGCCCTTCT CCCTCAGACC  
 TAGGAGTCCA GGGCCCCAGC CTCTCTCCC TCAGACCCAG GAGGAGTCCA GACCCAGTT CCTCTCCCT CAGACCCGGG  
 20 AGTCCAGCCC AGGCCCTCTCT CTCTCAGACC CGGAGTCCAG CCTGAGCTCT CTGCTTATC CTGCCCCAG GTGTTTGCGG  
 CCTGGTCTG GTCGTGTGTA GCCTGTGGCC AGATACAGCT GTGCGCCCTG GGGCACCACC TGGCCCCCTT CGAGTTTCCC  
 CAGACCCTCG GGGCGAGCTG GACAGCACCG TGCTCTGTAC CGCTCTCTC CTGGCGGACA CGCGGCAGCT GGCTGCACAG  
 CTGGTAGGAG AGACTGGGCT GGGGCCAGCA CAGGAGTGA AGGCAGAGAG GAACGGAGAG GAGTCTGCGG GCAGCCACTT  
 GGAAGGGGTT TGGGCTCTCA GTTGGCAGAG TGAGGGAGGG GAAGAGTTGG GGGCCTGGCG TGGGGATGG AGGGAGCCCC  
 25 GAGGCTGGGC AGGGGCCACC TCACAGCTTT TTTCCTCCCG AGAGGACAAA ATTCCAGCT GACGGGAGCT ACAACCTGGA  
 TTCCCTGCC ACCCTGGCCA TGAGTGCAAG GGCAGTGGGA GCTCTACAG TAAGGGCAAG GGAGTGGGCT GGGGACAAGG  
 TGGGAGGCG GCAGTGAAGG GGGCGGGGAG GATGAGGGG ACTGTCGGG GTTCTCTGA TGTCCCGCT CTATCCCCAG  
 CTCCAGGTTG TGTGACAAG GTCGCGAGCG GACCTACTGT CCTACTCTGC GCACGTGCAG TGGCTGCGCG GGGCAGGTGG  
 30 CTCTTCCCTG AAGACCCTGG AGCCCGAGCT GAGCACCTCG CAGGCCCGAC CAGGCCCGCT TGGACCGGCT GCTGCGCCGG CTGACGCTCC  
 TGGTATGTCC TGGCCCCAAG ACCTGACACC CCAGACCCCC ACCCTGGCC CCAAAATCCT GTGGCCTGAG TCCTTGAAGC  
 CTGAGACCCC AGACCCGAGT GCAACAGCCC CGCTCTGAGA CCTGACACC CTAACAGCCC GCTCTGAGAC CCGTACACCG  
 TAACAGCCCC GCTCTGAGAC CCTGACCTTA ACAGTCTGCT TCTGAGACCC TGACCCTGCA GTCCCAAGAT TCTGTGGCC  
 TGAGACCTCG AGGCCCTAGA CCCCCAAATC CTGCCAGAA ACTTCAAAT CTACCCAAAG ACCCTGAGAC CCTATCATCC  
 35 ATGACCTCAA AGTCCCCAGA TCCAGCCCC TAAGACCCAA GACCCATCC TGAAGCCCAA AGCCTTGAGA ATTCAAATCC  
 TCACCTCAAG ACTTGGAGAG CCGTGGCCCCA TGACATTGAA AACCATTGAC CTGGCCAGGC GTGGTGGCTC ACGCTGTAA  
 TCCAGCACT TGGGAGGCC GAGGCAAGTG GATCACTGA GTGCGGAGT TCAAGACCAG CCAGACCAA ATGTGAAAC  
 CCTGTCTTA CTAAGAAATAC AAAATTAGCC AGGCGTGGTG GTGCATGCT GTAATCCAG CTACTTGGGA GGCTGAGGCA  
 GGAGAATCGC TTGAACCTGG GAGGCGGAGG TTGCAGTGAG CCGAGATCGC ACCATTACAC TCCAGCCTGG GCAACAAGAG  
 CAAAACCTCC TCTCTCTCAA AAAAAAATAA AAAAAAATAA AAGAAAGAAA AGAAACCAT GGACCTCCAG ACCCTGAGAC  
 40 CCAAGTCCC AGCCCTGAGA TCCTGACATC TTAAGATCC CAGGCCCTAA CAGGCCCTAA GATACAAGAC CTTGACCCAA AGCCAGCCTT  
 GGGACCTGG CTGTACAAAC CCAAGACCTC CAGGACCTAG ACCCGAGGCC CTGAGGCCCT ATGTCTCACT CCAACATCG  
 AAAACCTGA CACCTCAGAT CCGTACGCTG CGCCTGTACG ACTCCAAGAC CCTCACTCC AAAGCCAGGC CCAAGGCCCT  
 GAGACAGAA GACTTCAAAC CCTGGTTCTT GGGCCTAACT CCAAGACCC TGGATCTCAA ATTCCAAT CTAGCTCTGA  
 45 GACTCCAGCC GTCACCCAG AGTTCTGAA CTTGAACCCA GAGACCCAT CTCTAAGACT TCAGCCTTGA GATGAGGCG  
 CTGACCCTAG ACTCGAGCCC ACAGACCTCA GATACTGTCT GTAAAACCCC AGCTCTGGTG GGGAGCAGTG GCTCACTCT  
 GTAATCCCAA GGCAGGGGAG GCCAAGGCAG AAGGACCTCT TGAGGCCATG AGTTTGAGAG AGCCTGGGCA GCATAGCAAG  
 ACTCTGTTTC TTAATTATTA TTATTATTAT TATTTTITG AGACAGAGTC TCGCGCTCTG TTGCCAGGC TAGAGTGCAA  
 TGGTGCCATT TCGGCTTGCT GGAACCTCCG CCTCTGGGC TCAAGCGATT CTCTGCTC TCCTCTCTGA AGCCTCTGGA  
 50 CTTCAGGTGC AACTGCCCAC ACCCGGATAA TTTTITGTA TTTTAGTAGA CACAGGGTTT CACCGTGTG CCCAGGCTGG  
 TCACAAACTC CTGAGCTCAG GCCATCCGCC CGCTCTGGGC TCCCAAAGCG CTGGGATAAC AGGCGTGACG CCGCGCTGG  
 GTCTTTAAT GTTCTAACAG CAGCGACAAC AACAAAACCC CAGCTCTGAG ATTCCAGCCC CGGCGACTCT AACAGTCCA  
 GGGCCGATCC CTCACCTAGA ACCGAGATGC CAGCCCTGAC TCCACAGACT TCACCCCAA CCCCACACT CAGCTCTGGA  
 AGCCGTCCT GACTCCAGCC TCCATTTTCG GAACCCACA GCCTGAAGAG CTCCCGGCT AAACACTTCA CCCCACGCGC  
 CACAGTCCCC CTGTGAATAT GCAGCCCCGA TCTAGCTGCA GCTCCACAGC ACCCTGCCG TGCACCCCG CTGCACCCCG  
 55 TACCTGTGAC TCACCTCTCT CACTCTCCCA CAGATGTCCC GCGTGGCCCT GCGCCAGCCA CCCCAGACC CCGCGGCGCC  
 CCGCTGGCG CCCCCCTCT CAGCCTGGGG GGGCATCAGG GCGGCCACG CCATCTGGG GGGGCTGCAC CTGACACTTG  
 ACTGGGCCCT GAGGGGACTG CTGCTGCTGA AGACTCGGCT GTGACCCGGG GCGCAAAGCC ACCACCGTCC TTCCAAAGCC  
 AGATCTTATT TATTTATTTA TTTCACTACT GGGGCGGAAA CAGCCAGGTG ATCCCCCGC CATTATCTCC CCTAGTTAG  
 AGACAGTCT TCCGTGAGGC CTGGGGGGCA TCTGTGCTT ATTATACTT ATTTATTCA GGAGCAGGGG TGGGAGGCAG  
 60 GTGACTCTCT GGGTCCCCGA GGAGGAGGGG ACTGGGGTCC CGGATTCTTG GGTCTCCAAG AAGTCTGTCC ACAGACTTCT  
 GCCTGGCTC TTCCCATCT AGGCCCTGGG AGGAACATAT ATTTATTTAT TAAGCAATTA CTTTTCATGT TGGGGTGGGG  
 ACGGAGGGGA AAGGGAAGCC TGGGTTTTG TACAAAATG TGAGAAACCT TTGTAGACA GAGAACAGGG AATTAATGT  
 GTCATACATA TCCACTTGAG GGCATTTTGT CTGAGAGCTG GGGCTGGATG CTTGGGTAAC TGGGGCAGGG CAGGTGGAGG  
 GGAGACCTCC ATTCAGGTGG AGGTCCCGAG TGGGCGGGG AGCGACTGG AGATGGGTG GTCACCCAGA CAGCTCTGTG  
 65 GAGGCAAGGT CTGAGCCTTG CCTGGGGCCC CGCACTGCAT AGGGCCGTTT GTTTGTTTTT TGAGATGGAG TCTCGCTCTG  
 TTGCTTAGGC TGGAGTGCAG TGAGGCAAT TAAGTCTCCA CCTCCGGGT TCAAGCAAT CTCTGCTCT CTCTGCTCT  
 AGCCTCCCGA TTAGCTGGGA TCACAGGTGT GCACCCCAT GCCAGCTAA TTAATTTATT CTTTTGTATT TTTAGTAGAG  
 ACAGGGTTTC ACCATGTGG CCAGGCTGTG TTCGAATCT TGACCTCAGG TGATCCTCT GCCTCGGCT CCAAAAGTGC  
 TGGGATTACA GGTGTGAGCC ACCACACCTG ACCCAATAGT TCTCAATAAA TATTTAATGG AAGGTTCAC AAGTCACTCT  
 70 GTGATCAACA GTACCCGATG GTGACAAAGC TCAAGGTCA AGTAGGTTCA TTAGGCTGT TTAGGCTGT GTTCACTTGA  
 AACAACTAG ATATCAACA GTGAGGGTTA AGCAACATGG TGCATCTGTG GATAGAACGC CACCCAGCCG CCGGAGCAG  
 GGAATGTCT TCAGGGAGGC TAAGGAGAGG GGCCTGTGTT GGAATATGAA AGATATCCTG ACATTGGCCA GGCATGGTGG  
 CTCACGCTGT TAATCTGGG ACITTTGGGAG GACAAGCGA GTGGATACCT GAAGTCCAAG AGTTTGAGAG CCGCTCGCA  
 75 GACATGGCAA AACCTGTCT CAAAAAGAA AGAATAGTGT CTGACATGA AACAGCAGGC TACAAAACCA CTGCATCTGT  
 TGATCCCAAT TTTGTGTTTT TCTTCTATA TATGGATTAA AACAAAAATC CTAAAGGAA ATACGCCAAA ATGTGACAA

TGACTGTCTC CAGGTCAAAG GAGAGAGGTG GGATGTGGG TGACTTTAA TGTGTATGAT TGTCTGTATT TTACAGAATT  
TCTGCCATGA CTGTGTATT TGCATGACAC ATTTTAAAAA TAATAAACAC TATTTTATA ATAACAGAA ATCAGCCTCC  
TCTCTCCAA AAATAAGCCC TCAGGAGGGG ACAAAGTTGA CCGCTGATTG AGCCTGTACG GGCTGTGCAC-3' (FRAG. NO:)(SEQ  
ID NO:11891)

#### 5 Human GM-CSF Nucleic Acid and Antisense Oligonucleotide Fragments

5'-CTTGBGCBGG BBGCTCTGGG GCBGGGBGCT GGCBBGGGCC BGGGGGGTGG CTTCCTGCBC TGTCCBGBGT GCBCTGTGCC  
BCBGCBCBGG CTGCBGGGCC BTCBGCTTCB TGGGGCTCTG GGTGGCBGGT CCBGCCBTGG GTCTGGGTGG GGCTGGGCTG  
CBGGCTCCGG GCGGTCCBGGCBTGGGTCTG GGGGCTGGG CTGCBGGCTC CCGGCCGGCG GGTGCGGGCT GCGTGTGGG  
GGCTGCCCCG CAGGCCCTGC GGTCBGGCCB TGGTCTGGG GGCTGGGCTG CBGGCTCCGG GCGGGCGGGT GCGGCTGCG

10 TGCTGGGGGC TGCCCCGAG GCCCTGC-3' (FRAG. NO:1847) (SEQ ID NO:11229)

5'-GBGCBGG BBG-3' (FRAG. NO:1848) (SEQ ID NO:11230)

5'-GCCBCBGGCBGCGC-3' (FRAG. NO:1849) (SEQ ID NO:11231)

5'-GGG TGC GGG C-3' (FRAG. NO:1850) (SEQ ID NO:11232)

5'-GGT CCB GCC BTG GGT CTG GG-3' (FRAG. NO:1300)(SEQ ID NO:10678)

15 5'-GGC TGG GCT GCB GGC TCC GG-3' (FRAG. NO:1301)(SEQ ID NO:10679)

5'-GCG GGC GGG TGC GGG CTG CGT GCT GGG-3' (FRAG. NO:1302)(SEQ ID NO:10680)

5'-GGC TGC CCC GCA GGC CCT GC-3' (FRAG. NO:1303)(SEQ ID NO:10681)

5'-CTTGBGCBGG BBGCTCTGGG GCBGGGBGCT GGCBBGGGCC BGGGGGGTGG CTTCCTGCBC TGTCCBGBGT GCBCTGTGCC  
BCBGCBCBGG CTGCBGGGCC BTCBGCTTCB TGGGGCTCTG GGTGGCBGGT CCBGCCBTGG GTCTGGGTGG GGCTGGGCTG

20 CBGGCTCCGG GC-3' (FRAG. NO:1851) (SEQ ID NO:11233)

#### Human Tumor Necrosis Factor ( Antisense Oligonucleotide Fragments

5'-GCBCCGCGCTG GBGCCCTGGG GCGCCCTGT CTCTTGGGG BGCCTCTCT CGGCCBGGCTC CBCGTCCCGG BTCBTGCTTT  
CBGTGCTCBT GGTGTCTTT CCBGGGGGBG GBGGGGCTGG TCCTCTGCTG TCCTTGCTGG TGCTCBTGGT GTCCTTTCCG  
CCCTGGGGCC CCCCTGTCTT CTGGGGCTT CTCCCTCTG GGGGCGGTCT CTCTCCCTCT CTGCGTCTC TCTCTTCTC

25 TCTCTCTCTT CCCCTTTCCC GCTCTTCTG TCTCGGTGTC TGGTTTCTC TCTCCGCTGG CTGCTGTCT GGCCTGCGCT  
CTTGCGCTGT GCTGTCTCT CTCCGTTCC GTCTCTCTCT GTCTGTGCGC CCTCTGGGG TCTCCCTCTG GGTGTGGTCT  
TTGTGTCTG GGTGTGGCTC CGTGTCTCCB GTGCTCBTGG TGTCCGCTGB GGGBCGCTCT GCTGGCGCTG GTCCTCTGCTGTC

CTTGCTGGTG CTCBTGGTGT CCTTTCGCC CTGGGGCCCC CCGTCTCTT TGGGGCTCT TCCTCTGGG GGCGCTCTC  
TCTCCCTCTC TTGCGTCTCT CTCTTCTCT CTCTCTCTC CCCTTTCGG CTCTTCTGT CTGCGTGTCT GGTCTTCTCT

30 CTCGCTGGC TGCTGTCTG GCTGCGCTC TTGGCCTGTG CTGTCTCTC TCCGTTCCCT GTCCTCTCT TCTGTGCGCC  
CCTCTGGGGT CTCCCTCTGG CGTGGTGGTC TTGTGCTTG GGCTGGGCTC CGTGTCTCCB GTGCTCBTGG TGTCCGCTGB

GGGBGCTCT GCTGGC-3' (FRAG. NO:1852)(SEQ ID NO:11234)

5'-GGGGCCCCC-3' (FRAG. NO:1853) (SEQ ID NO:11235)

5'-GGG GGC CG TCT-3' (FRAG. NO:1854) (SEQ ID NO:11236)

35 5'-CCBGGGGGBG GBGGGGCTGG-3' (FRAG. NO:1855) (SEQ ID NO:11237)

5'-GCBCCGCGCTG GBGCCCTGGG GCGCCCTGT CTCTTGGGG BGCCTCTCT CGGCCBGGCTC CBCGTCCCGG BTCBTGCTTT  
CBGTGCTCBT GGTGTCTTT CCBGGGGGBG GBGGG-3' (FRAG. NO:1304) (SEQ ID NO:10682)

5'-GCT GGT CCT CTG CTG TCC TTG CTG GTG CTC BTG GTG TCC TTT CC GCC CTG GGG CCC CCC TGT CTT CTT GGG G CCT  
CTT CCC TCT GGG GGC CG TCT CTC TCC CTC TCT TGC GTC TCT C TCT TTC TCT CTC TCT CTT CCC C TTT CCC GCT CTT TCT

40 GTC TC GGT GTC TGG TTT TCT CTC TCC GCT GGC TGC CTG TCT GGC CTG CGC TCT T GGC CTG TGC TGT TCC TCC TCC GGT  
TCC TGT CCT CTC TGT CTG TC GCC CCC TCT GGG GTC TCC CTC TGG C GTG GTG GTC TTG TTG CTT GGG CTG GGC TCC GTG

TCT C CBG TGC TCB TGG TGT CC-3' (FRAG. NO:1305) (SEQ ID NO:10683)

5'-GCT GBG GGB GCG TCT GCT GGC GCT GGT CCT CTG CTG TCC TTG CTG GTG CTC BTG GTG TCC TTT CC GCC CTG GGG CCC  
CCC TGT CTT CTT GGG G CCT CTT CCC TCT GGC GGC CG TCT CTC TCC CTC TCT TGC GTC TCT C TCT TTC TCT CTC TCT CTT

45 CCC C TTT CCC GCT CTT TCT GTC TC GGT GTC TGG TTT TCT CTC TCC GCT GGC TGC CTG TCT GGC CTG CGC TCT T GGC CTG  
TGC TGT TCC TCC TCC GGT TCC TGT CCT CTC TGT CTG TC GCC CCC TCT GGG GTC TCC CTC TGG C GTG GTG GTC TTG TTG

CTT GGG CTG GGC TCC GTG TCT C CBG TGC TCB TGG TGT CC GCT GBG GGB GCG TCT GCT GGC-3'(FRAG. NO:1306)(SEQ ID  
NO:10684)

5'-GCT GGT CCT CTG CTG TCC TTG CTG-3' (FRAG. NO:1655) (SEQ ID NO:11033)

50 5'-GTG CTC BTG GTG TCC TTT CC-3' (FRAG. NO:1656)(SEQ ID NO:11034)

5'-GCC CTG GGG CCC CCC TGT CTT CTT GGG G-3' (FRAG. NO:1657)(SEQ ID NO:11035)

5'-CCT CTT CCC TCT GGG GGC CG-3' (FRAG. NO:1658)(SEQ ID NO:11036)

5'-TCT CTC CTC TCT TGT GTC TCT C-3' (FRAG. NO:1659)(SEQ ID NO:11037)

5'-TCT TTC TCT CTC TCT CTT CCC C-3' (FRAG. NO:1660)(SEQ ID NO:11038)

55 5'-TTT CCC GCT CTT TCT GTC TC-3' (FRAG. NO:1661)(SEQ ID NO:11039)

5'-GGT GTC TGG TTT TCT CTC TCC-3' (FRAG. NO:1662)(SEQ ID NO:11040)

5'-GCT GGC TGC CTG TCT GGC CTG CGC TCT T-3' (FRAG. NO:1663)(SEQ ID NO:11041)

5'-GGC CTG TGC TGT TCC TCC-3' (FRAG. NO:1664)(SEQ ID NO:11042)

5'-TCC GGT TCC TGT CCT CTC TGT CTG TC-3' (FRAG. NO:1665)(SEQ ID NO:11043)

60 5'-GCC CCC TCT GGG GTC TCC CTC TGG C-3' (FRAG. NO:1666)(SEQ ID NO:11044)

5'-GTG GTG GTC TTG TTG CTT-3' (FRAG. NO:1667)(SEQ ID NO:11045)

5'-GGG CTG GGC TCC GTG TCT C-3' (FRAG. NO:1668)(SEQ ID NO:11046)

5'-CBG TGC TCB TGG TGT CC-3' (FRAG. NO:1669)(SEQ ID NO:11047)

5'-GCT GBG GGB GCG TCT GCT GGC-3' (FRAG. NO:1670)(SEQ ID NO:11048)

#### 65 Human Leukotriene C4 Synthase Nucleic Acids and Antisense Oligonucleotide Fragments

5'-CTCGGTBGGC GCGCTCBBBC TCGGGTGGGC CGGTGTGGBG CGGCGGCBBCB CGCGGBBGGC CCTGCGCGCC GBGBTCBCCTG  
CBGGGBBGGG TBGGCTTGCB GCBGGBTCC CBGGGGGGT BCBGCBGCCB GTBGBGCTBC CTCGTCTTC BTGGTBCCGT

CGGTGTGGT GCBGCGGCTG TGTGTGBBG CBGCTGGGC CCGCTCTGCT GCTCCTCGTG CCGCCTCGCT CTCA TGG TA  
CCGTGCGGTG GGTGGCCTCG GGTGGGCGG TGGTGGGGCG CGCGCGCTCG CGTGGCTCCG GCTCTCTTT CCCGGCTCCGT

70 CGGCCCGGGG GCCTTGGTCT CCCTCGTCT TCBTGGTBCC G-3' (FRAG. NO:1856) (SEQ ID NO:11238)

5'-GCB GCBGGBC-3' (FRAG. NO:1857) (SEQ ID NO:11239)

5'-CCCGGCTCCG-3' (FRAG. NO:1858) (SEQ ID NO:11240)

5'-CGGCCCGGG GCC-3' (FRAG. NO:1859) (SEQ ID NO:11241)

5'-CB CGCGG-3' (FRAG. NO:1860) (SEQ ID NO:11242)



5'-GCC CCG TCT GCT GCT CCT CGT GCC G-3' (FRAG. NO:1307)(SEQ ID NO:10685)  
 5'-CCT CGT CCT TCA TGG TAC CGT CGG TGT GGT GGC-3' (FRAG. NO:1308)(SEQ ID NO:10686)  
 5'-CTC GGG TGG GCC GGT GGT G-3' (FRAG. NO:1309)(SEQ ID NO:10687)  
 5'-GGG CGC GCG CGC TCG CGT-3' (FRAG. NO:1310)(SEQ ID NO:10688)  
 5'-GGC TCC GGC TCT TCT TTC CCG GCT CCG TCG GCC CGG GGG CCT TGG TCT C-3'(FRAG.NO:1311)(SEQ ID NO:10689)  
 5'-CCT CGT CCT TCB TGG TBC CG-3' (FRAG. NO:1312)(SEQ ID NO:10690)  
 5'-CTCGGTBGGC GCGCTCGBBC TCGGGTGGGC CGGTGGTGBG CGGCGGCBBCB CGCGGBBGGC CCTGCGCGCC GBGBTCBCCTG  
 CBGGGBBGG TBGGCTGCB GCBGGBCCTC CBGGBGGGTG BCBGCBGCCB GTBGBGCTBC CTCGTCTTC BTGGTBCCGT  
 CGGTGTGGTG GCBGGGGCTG TGTGTGBBGG CGBGCTGG-3' (FRAG.NO:1861) (SEQ ID NO:11243)

#### Human Endothelin-1 Nucleic Acids and Antisense Oligonucleotide Fragments

5'-BCCGGGCGBG CCGCBGGGT GGBCTGGGBG TGGTTTCTC CCGCCGTTC TCBCCBCCG CGCTGBGCTC BCGCCTBBG  
 BCTGCTGTTT CTGGBGCTCC TTGGCBGGC BCBBCBGC BGGGBBBBT CBTGBGCBBC TBBTCCBTTC TGBBBBBBBG  
 GGBTCBBBB CCTCCGTTT CCGGTCGCC TGGCGCGCC TGGCGGTTT TCGTGGGTTT CTCCCGCCG TTCTCCGGT  
 TGTGCTTT GTGGGCTTCT TGTCTTTT TCTGTTCTT TCCTGCTTG CGTCTTTTC TTCTTTGTG CTCGGTTGTG  
 GTCCGCTGG TCTTTGCC TGTGTGTTT TGTGCTCGT TCGCTGGCG CGCGCTGCGG GTTCCTCGT GGTTCCTCC  
 CGCCGTTCTC CGGTCTGTT CTTTGTGGG CTTCTGTCT TTTTGGCTGT TCTTTCTCT CTGGCGTCT TTTCTTTCT  
 TTGTGCTCG TGTGGGTCC GCTGTCCTT TGCCCTGTGT GTTCTGCTG-3' (FRAG. NO:1862) (SEQ ID NO:11244)

5'-CCGGCGGBG CCGCBGGGT GGB-3' (FRAG. NO:1863) (SEQ ID NO:11245)

5'-CCGCCBGGG-3' (FRAG. NO:1864) (SEQ ID NO:11246)

5'-GGCGCGCGC-3' (FRAG. NO:1865) (SEQ ID NO:11247)

5'-GTGGGTCCG-3' (FRAG. NO:1866) (SEQ ID NO:11248)

5'-CCCCTCGCCTGGCGC-3' (FRAG. NO:1313)(SEQ ID NO:10691)

5'-GCGCTCGGGTTCTCTC-3' (FRAG. NO:1314)(SEQ ID NO:10692)

5'-GTGGGTTTCTCCCGCGTTCTC-3' (FRAG. NO:1315)(SEQ ID NO:10693)

5'-CGGTCTGTTGCCCTTTGTGGG-3' (FRAG. NO:1316)(SEQ ID NO:10694)

5'-CTTCTGTCTTTTGGCT-3' (FRAG. NO:1317)(SEQ ID NO:10695)

5'-GTTCTTTCTGCTTGGC-3' (FRAG. NO:1318)(SEQ ID NO:10696)

5'-GTTCTTTCTTTCTT-3' (FRAG. NO:1319)(SEQ ID NO:10697)

5'-TGTGCTCGGTTGTGGTC-3' (FRAG. NO:1320)(SEQ ID NO:10698)

5'-CGCTGGTCCTTTGCC-3' (FRAG. NO:1321)(SEQ ID NO:10699)

5'-CTGTGTGTTTCTGCTG-3' (FRAG. NO:1322)(SEQ ID NO:10700)

5'-CCCCTCGCCTGGCGC-3' (FRAG. NO:1323)(SEQ ID NO:10701)

5'-GCGCTCGGGTTCTCTC-3' (FRAG. NO:1324)(SEQ ID NO:10702)

5'-GTGGGTTTCTCCCGCGTTCTC-3' (FRAG. NO:1325)(SEQ ID NO:10703)

5'-CGGTCTGTTGCCCTTTGTGGG-3' (FRAG. NO:1326)(SEQ ID NO:10704)

5'-CTTCTGTCTTTTGGCT-3' (FRAG. NO:1327)(SEQ ID NO:10705)

5'-GTTCTTTTCTGCTTGGC-3' (FRAG. NO:1328)(SEQ ID NO:10706)

5'-GTTCTTTCTTTCTT-3' (FRAG. NO:1329)(SEQ ID NO:10707)

5'-TGTGCTCGGTTGTGGTC-3' (FRAG. NO:1330)(SEQ ID NO:10708)

5'-CGCTGGTCCTTTGCC-3' (FRAG. NO:1331)(SEQ ID NO:10709)

5'-CTGTGTGTTTCTGCTG-3' (FRAG. NO:1332)(SEQ ID NO:10710)

#### Endothelin Receptor ET-B Nucleic Acids and Antisense Oligonucleotide Fragments

5'-GCCCTGTCGG GCGGGAAGCC TCTCTCTCT CCCCAGATC CGCGACAGGC CGCAGGCAAG AACCAGCGCA ACCAGGGCGC  
 GTCCGACAG ACTTGGAGGC GGCTGCATGC TGCTACCTGC TCCAGAAGCG TCCGGTGGCC GCCGCGCC CTGTGGGGC  
 GBBGGCTCT CTCCTCTCC CBGTTCCGCG BCBGGCCGB GGBBGBBCC BGCGBBCCB GGGCGCGTCC GCBGBBCTT  
 GBBGGCGGCT GCBTGTCTCT BCCTGCTCGGGC GGBBGGCTCC GTGGCCGCG CGCGTCCGT GGGCGCGCG CCTCTCTCT  
 CTCCCGTGG CCCTGTCGGG CGGGTCTGC CGTCTGTCT CTTTCTCTT TGCTGTCTT TCTTCCCGTC TCTGCTTT-3' (FRAG.  
 NO: 1867) (SEQ ID NO:11249)

5'-CGGGCG GBBGCC-3' (FRAG. NO: 1868) (SEQ ID NO:11250)

5'-CGGGCGGG-3' (FRAG. NO: 1869) (SEQ ID NO:11251)

5'-CCGCBGBBC-3' (FRAG. NO: 1870) (SEQ ID NO:11252)

5'-GCGTCCGGTGGCGCGC-3' (FRAG. NO:1333)(SEQ ID NO:10711)

5'-GCCTCTCTCTCTCTCC-3' (FRAG. NO:1334)(SEQ ID NO:10712)

5'-GTGGCCCTGTGCGGCGGG-3' (FRAG. NO:1335)(SEQ ID NO:10713)

5'-TCCTGCGTCTCTCTCTT-3' (FRAG. NO:1336)(SEQ ID NO:10714)

5'-TCTTTTGTCTGTGT-3' (FRAG. NO:1337)(SEQ ID NO:10715)

5'-CTTCCGCTCTCTCTT-3' (FRAG. NO:1338)(SEQ ID NO:10716)

5'-GCCCTGTCGG GCGGGAAGCC TCTCTCTCT CCCCAGATC CGCGACAGGC CGCAGGCAAG AACCAGCGCA ACCAGGGCGC  
 GTCCGACAG ACTTGGAGGC GGCTGCATGC TGCTACCTGC TCCAGAAGCG TCCGGTGGCC GCCGCG-3' (FRAG. NO: 1871) (SEQ  
 ID NO:11253)

5'-GCCCTGTCGG GCGGGBBGC TCTCTCTCT CCCCAGATC CGCGACAGGC CGCAGGCAAG AACCAGCGCA ACCAGGGCGC  
 GTCCGCBGB BCTTGGBGC GGCTGCBTGC TGCTBCTGC TCCBGBBGC TCCGGTGGCC GCCGCG-3' (FRAG. NO: 1872) (SEQ  
 ID NO:11254)

#### Endothelin ETA Receptor Nucleic Acids and Antisense Oligonucleotide Fragments

5'-GTCTGTCTC CCGTCTCT CCACTGCTT CTCCGGGGG CTTCCCGGC TCCGGTGGC CGGTGTCCCG GGCTCCGGG  
 CGGCGCGGC TTCGGTGGC GGTGGGTGGC GCGGGCTGCC GGGTCCGCG GCGCCTGGC CCCTGTGCT GCTTTTGTCT  
 TGTTCGTTT TGGTGTCTC GGTCTGTGT GTGGTGTGT TGTCTTCTT TGGGTGTGG CCTTGGCGT TGGTGTGG  
 GCCCTTGGG GCTTGGCTT CTGGCTGCT TGCTCTCC ACTGCTCT CCCGGGGCT TCCCGGCTT  
 CGGGTGGCC GTGTCCCGG CTCCGGCGCG GCGGCGGCTT CGGCTGCGG TGGGTGGCG GGGTGGCG GTCCGCGCG  
 CGCCTGGGC CTGTGCTGC TTTTGTCTG TTCCGTTCT GCTGCTCGG TGTGTGTGT GTTGTGTGT TTTCTCTG  
 GGTGTGGGC TTGCGGTTT GGCTGTGGG CCTTGGGCG CTGGCTCTT GGCTCCAT CCACATGATT GCTTAGATT  
 GTGCTGATC TCTAGGATT ATCACTGATT ACACATCAA CAGTGCCAG CAAAAGGAT GCCCTAGGC AAAGGTTTC  
 CATCTGAGG CAAATTTAG GACBTCCB BTGTTGCTT BGBTTGTG TGTCTCTC BGGTTTBCB CTGTTTBCB

BTCCBBCCBG TGCCBGCCBB BBGGBTGCCC TGBGGCBBBG GGTTCBCBTC TTGBGGCBBB TTTGBGGB-3' (FRAG. NO:1873)  
 (SEQ ID NO:11255)  
 5'-GBGGCBBBGGG-3' (FRAG. NO:1874) (SEQ ID NO:11256)  
 5'-GCCBGCCBB BBGGB-3' (FRAG. NO:1875) (SEQ ID NO:11257)  
 5'-CGCCTGGGCC C-3' (FRAG. NO:1876) (SEQ ID NO:11258)  
 5'-GTCTGTCTCCCGCTCTCCTCC-3' (FRAG. NO:1339)(SEQ ID NO:10717)  
 5'-ACTGCTTCTCCCGGGG-3' (FRAG. NO:1340)(SEQ ID NO:10718)  
 5'-GCTTCCCCGGCTTC-3' (FRAG. NO:1341)(SEQ ID NO:10719)  
 5'-GGGTGGCCGGTGTCCCGGGCTCCGGCGCGCGGC-3' (FRAG. NO:1342)(SEQ ID NO:10720)  
 5'-GGCTTCGGCTGC-3' (FRAG. NO:1343)(SEQ ID NO:10721)  
 5'-GGGTGGGTGGCGCGG-3' (FRAG. NO:1344)(SEQ ID NO:10722)  
 5'-GCTGCCGGGTCCGCGCGCGCCTGGGCC-3' (FRAG. NO:1345)(SEQ ID NO:10723)  
 5'-CTTGTGCTGCTTTT-3' (FRAG. NO:1346)(SEQ ID NO:10724)  
 5'-TGCTTGTTCCTTC-3' (FRAG. NO:1347)(SEQ ID NO:10725)  
 5'-TGGCTGCTCCGGTCTGTGTTGTGGTTGTTT-3' (FRAG. NO:1348)(SEQ ID NO:10726)  
 5'-TTTCTTCTGGGTGTGGG-3' (FRAG. NO:1349)(SEQ ID NO:10727)  
 5'-CCTTGGGTTTGG-3' (FRAG. NO:1350)(SEQ ID NO:10728)  
 5'-CTGTGGGCCCTTTG-3' (FRAG. NO:1351)(SEQ ID NO:10729)  
 5'-GGGCCTTGGCTTCTGGCTC-3' (FRAG. NO:1352)(SEQ ID NO:10730)  
 5'-CATCCACATG ATTGCTTAGA TTTGTGCTGT ATCTCTCAGG ATTATCACTG ATTACACATC CAACCACTGC CAGCCAAAAG  
 GATGCCCTGA GGCAAGGGT TTCCATCTTG AGGCAATTT GAGGA-3' (FRAG. NO:1353) (SEQ ID NO:10731)  
 5'-CBTCCBCBTG BTTGCTTBGB TTTGTGCTGT BTCTCTCBGG BTTBCTCBTG BTTBCTCBTC CBBCCBTGC CBGCCBBBGG  
 GBTGCCCTGB GGCBBBGGGT TTCCBTCTTG BGGCBBBTTT GBGGB-3' (FRAG. NO:1354)(SEQ ID NO:10732)  
 Endothelin Receptor A Nucleic Acid and Antisense Oligonucleotide Fragments  
 5'-GCCACCATGG AAACCCCTTG CCTCAGGGCA TCCTTTTGGC TGGCACTGGT TGGATGTGTA ATCAGTGATA ATCCTGAGAG  
 ATACAGCACA AATCTAAGCA ATCATGTGGA TGATTTTACC ACTTTTCGTG GCACAGAGCT CAGCTTCCTG GTTACCACTC  
 ATCAACCCAC TAATTGGTC CTACCCAGCA ATGGCTCAAT GCACAACTAT TGCCACAGC AGACTAAAAA TACTTCAGCT  
 TTCAAATACA TTAACACTGT GATATCTGT ACTATTTTCA TCGTGGGAAT GGTGGGAAT GCAACTCTGC TCAGGATCAT  
 TTACAGAAC AAATGTATGA GGAATGGCCC CAACGCGCTG ATAGCCAGTC TTGCCCTTGG AGACCTTATC TATGTGGTCA  
 TTGATCTCCC TATCAATGTA TGGCTGGCG CTGGCCTTTT GATCACAATG ACTTTGGCGT ATTTCTTTC AAGCTGTTC  
 CCTTTTTCGA GAAGTCTCTG GTGGGGATCA CCGTCTCAA CCTCTGCGCT CTTAGTGTG ACAGGTACAG AGCAGTTGCC  
 TCCTGGAGTC GTGTTACGGG AATTGGGATT CCTTTGGTAA TGCCATTGA AATTGCCTCC ATCTGGATCC TGTCTTTAT  
 CCTGGCCATT CTGAAGCGA TTGGCTTCGT CATGGTACCC TTGAAATATA GGGGTGGACA GCATAAAACC TGTATGCTCA  
 ATGCCACATC AAAATTCATG GAGTTCTACC AAGATGTAAG GGACTGGTG CTCTCGGGT TCTATTCTG TATGCCCTTG  
 GTGTGCACTG CGATCTTCTA CACCCTCATG ACTGTGAGA TGGTGAACAG AAGGAATGGC AGCTTGAGAA TTGCCCTCAG  
 TGAACATCTT AAGCAGCGTC GAGAAGTGGC AAAACAAGTT TCTGCTTGG TTGTAATTT TGTCTTTTC TGGTTCCTC  
 TTCAATTAAG CCGTATATTG AAGAAAACCTG TGTATAACGA GATGGACAAG AACCAGATGTG AATTACTTAG TTTCTTACTG  
 CTATGGATT ACATCGGTAT TAACITGGCA ACCATGAATT CATGTATAAA CCCCATAGCT CTGTATTTTG TGAGCAAGAA  
 ATTTAAAAAT TGTTCCTAGT CATGCCCTG CTGCTGCTGT TACCAGTCCA AAAGTCTGAT GACCTCGGTG CCCATGAACG  
 GAACAAGCAT CCAAGTGAAG AACCACGATC AAAACAACCA CAACACAGAC CGAGCAGACC ATAAGGACAG CATGAACCTGA  
 CCACCCCTAG AAGCACTCCT GAATTCGGGA AAAAGTGAAG GTGTAAGAGC AGCACAAGTG CAATAAGAGA TATTTCTCA  
 AATTGCGCTC AAGATGGAAA CCGTTTGCCT CAGGGCATCC TTTTGGCTGG CACTGGTTGG ATGTGTAATC AGTGATAATC  
 CTGAGAGATA CAGCACAAT CTAAGCAATC ATGTGGATGA TTTCAACACT TTTCTGGTGA CAGAGCTCAG CTTCTGTGT  
 ACCATCATC AACCCACTAA TTTGGTCTA CCCAGCAATG GCTCAATGCA CAACATTTGC CCACAGCAGA CTAAATTTAC  
 TTCAGCTTTC AAATACATTA ACATGTGAT ATCTTGTACT ATTTTCATCG TGGGAATGGT GGGGAATGCA ACTCTGCTCA  
 GGATCATTTA CCAGAACAAA TGTATGAGGA ATGGCCCCAA CGCGCTGATA GCCAGTCTTG CCTTGGAGA CCTTATCTAT  
 TGGTGCATTG ATCTCCCTAT CAATGTATTT AAGCTCTGG GTGGCGCTG GCCTTTTGTAT CACAATGACT TTGGCGTATT  
 TCTTTGCAAG CTGTTCCCT TTTTGCAGAA GTCTCTGGTG GGGATCACCG TCCTCAACCT CTGCGCTCTT AGTGTGACA  
 GGTACAGAGC AGTTGCCTCC TGGAGTCGTG TTCAGGGAAT TGGGATTCCT TTGGTAACTG CCATTGAAAT TGTCTCCATC  
 TGGATCTGT CTCTTATCCT GGCCATTCCT GAAGCGATTG GCTTCGTCT GGTACCCCTT GAATATAGGG GTGAACAGCA  
 TAAAACCTGT ATCTCAATG CCACATCAAA ATTCATGAG ATTCACCAAG ATGTAAAGGA CTGGTGCTC TCGGGTTCT  
 ATTTCTGTAT GCCTTGGTG TGCATGCGA TCTTCTACAC CCTCATGACT TGTGAGATGT TGAACAGAAG GAATGGCAGC  
 TTGAGAAATG CCTCAGTGA ACATCTTAAG CAGCGTCGAG AAGTGCCAAA AACAGTTTTC TGCTTGGTGT TAATTTTTC  
 TCTTTGCTGG TTCCCTCTTC ATTTAAGCCG TATATTGAAG AAACTGTGT ATAACGAGAT GGACAAGAAC CGATGTGAAT  
 TACTTAGTTT CTACTGCTC ATGGATTACA TCGGTATTA TCTGGCAACC ATGAATTCAT GTATAAACCC CATAGCTCTG  
 TATTTTGTGA GCAAGAAAT TAAAAATTGT TTCCAGTCAT GCCTCTGCTG CTGCTGTTAC CAGTCCAAAA GTCTGATGAC  
 CTCGGTCCCC ATGAACGGAA CAAGCATCCA GTGGAAGAAC CACGATCAAA ACAACCACAA CACAGACCGG AGCAGCCATA  
 AGGACAGCAT GAAGTAGCA CCCTTAGAAG CACTCCTCGG TACTCCATA ATCCTCTCGG AGAAAAAAT CACAAGGCAA  
 CTGTGATGCC GGAATCTCT TCTGTATCC TTCTCCTTA ATTCATCCC ACACCAAGA AGAAATGCTT TCCAAAACCG  
 CAAGGGTAGA CTGGTTTATC CACCCACAAC ATCTACGAAT CGTACTTCT TAATTGATCT AATTTACATA TCTGCGTGT  
 TGTATTACG ACTAAAAAAT GGTGGGAGCT GGGGGAGAAT GAAGACTGTT AAATGAAACC AGAAGGATAT TTAATCTTT  
 TGCATGAAAA TAGAGCTTTC AAGTACATGG CTAGCTTTTA TGGCAGTTCT GGTGAATGTT CAATGGGAAC TGTACCACTT  
 CAAGTCACTT TAATTGAAA TGTCAATTGG TGCCAGTATC CCGAATTC GAATTCGGGA AAAAGTGAAG GTGTAAGAGC  
 AGCACAAGTG CAATAAGAGA TATTTCTCA AATTGCGCTC AAGATGGAAG CCCTTTCCT CAGGGCATCC TTTTGGCTGG  
 CACTGGTTTG ATGTGTAATC AGTGATAATC CTGAGCAAT CTAAGCAATC ATGTGATGA TTTCACTCAT TTTCACTCAT  
 TTTCTGTCAG CAGAGCTCAG CTTCTGCTG ACCACTCATC AACCCTACTA TTTGGTCTA CCCAGCAATG GCTCAATGCA  
 CAACATTTGC CCACAGCAGA CTAAAAATTAC TTCAAGCTTTC AAATACATTA ACATGTGAT ATCTTGTACT ATTTTCATCG  
 TGGGAATGGT GGGGAATGCA ACTCTGCTCA GGATCATTTA CCAGAACAAA TGTATGAGGA ATGGCCCCAA CGCGCTGATA  
 GCGAGCTCTG CCTTTGAGGA CTTATCTAT GTGGTCAATG GTTCCCTAT CAATGTATTT AAGCTGCTG TCGGGCGCTG  
 GCCTTTTGTAT CACAATGACT TTGGCGTATT TCTTTGCAAG CTGTTCCCT TTTTGCAGAA GTCTCTGGTG GGGATCACCG  
 TCCTCAACCT CTGCGCTCTT AGTGTGACA GGTACAGAGC AGTTCCTCC TGGAGTCGTG TTCAGGGAAT TGGGATTCCT  
 TGTGTAACCT CCAATGAAAT TGTCTCCAT TGAATCAAGT TGGATCAATG CCACATCAAA ATTCATGGAG TTTCACTCAT  
 GGTACCCCTT GAATATAGGG GTGAACAGCA TAAAACCTGT ATTTCTGTAT GCCTTGGTG TGCATGCGA TCTTCTACAC CCTCATGACT  
 ATGTAAAGGA CTGGTGGCTC TTCGGGTTCT ATTTCTGTAT GCCTTGGTG TGCATGCGA TCTTCTACAC CCTCATGACT

TGTGAGATGT TGAACAGAAG GAATGGCAGC TTGAGAATTG CCTCAGTGA ACATCTTAAG CAGCGTCGAG AAGTGGCAAA  
 AACAGTTTTT TGCTTGGTTG TAATTTTTGC TCTTTGCTGG TTCCCTCTTC ATTTAAGCCG TATATTGAAG AAAACTGTGT  
 ATAACGAGAT GGACAAGAAT CGATGTGAAT TACTTAGTTT CTACTGCTC ATGGATTACA TCGGTATTAA CTTGGCAACC  
 5 ATGAATTCAT GTATAAACC CATAGCTCTG TATTTTGTA GCAAGAAAT TAAAAATTGT TTCCAGTCAT GCCTCTGCTG  
 CTGCTGTTC CAGTCCAAAA GTCTGATGAC CTCGGTCCCC ATGAACGGAA CAAGCATCCA GTGGAAGAAC CACGATCAAA  
 ACAACCACAA CACAGACCGG AGCAGCCATA AGGACAGCAT GAAGTACCA CCTTAGAAG CACTCCTCGG TACTCCATA  
 ATCCTCTCGG AGAAAAAAT CACAAGGCAA CTGTGAGTCC GGAATCTCT TCTCTGATCC TTCTTCTTA ATTCCTCCC  
 ACACCAAGA AGAAATGCTT TCCAAAACCG CAAGGGTAGA CTGGTTTATC CACCCACAAC ATCTACGAAT CGTACTCTT  
 TAATTGATCT AATTACATA TTCTGCGTGT TGTATTACG ACTAAAAAT GGTGGGAGCT GGGGAGAAT GAAGACTGTT  
 10 AAATGAAACC AGAAGGATAT TACTACTTT TGCATGAAAA TAGAGCTTTC AAGTACATGG CTAGCTTTTA TGGCAGTTCT  
 GGTGAATGTT CAATGGGAAC TGGTACCAT GAACTTTAG AGATTAACGA CAAGATTTTC TACTTTTTTT AAGTATTTT  
 TTTGTCCTTC AGCCAAACAC AATATGGGCT CAAGTCACTT TATTGAAA TGTCATTGG TGCCAGTATC CCGAATTC-3' (FRAG.  
 NO: ) (SEQ ID NO:12383)  
 5'-GAATTCGGGA AAAAGTGAAG GTGTAAGGC AGCACAAGTG CAATAAGAGA TATTTCTCA AATTTGCCTC AAGATGGAAA  
 15 CCCTTTGCCT CAGGGCATCC TTTTGGCTGG CACTGGTTGG ATGTGTAATC AGTGATAATC CTGAGAGATA CAGCACAAT  
 CTAAGCAATC ATGTGGATGA TTACCACT TTTCTGGGCA CAGAGCTCAG CTCTCTGGTT ACCACTCATC AACCCACTAA  
 TTTGGTCTTA CCCAGCAATG GCTCAATGCA CAACTATTGC CCACAGCAGA CTAAAAATTAC TTCAGCTTTC AAATACATTA  
 ACACGTGAT ATCTTGATCT ATTTTCATCG TGGGAATGGT GGGGAATGCA ACTCTGCTCA GGATCATTTA CCAGAACAAA  
 20 TGTATGAGGA ATGGCCCCAA CGCGCTGATA GCCAGTCTTG CCTTGGAGA CCTTATCTAT GTGGTCATTG ATCTCCCTAT  
 CAATGTATTT AAGCTGTCTG CTGGGCGCTG GCCTTTTAT CACAATGACT TTGGCGTATT TCTTTGCAAG CTGTTCCCTC  
 TTTTGCAGAA GTCTCTGGTG GGGATCACCG TCCTCAACCT CTGCGCTCTT AGTGTGACA GGTACAGAGC AGTTGCCTCC  
 TGGAGTCGTG TTAGGGAAT TTGGATTCTT TTGTAACTG CCATTGAAAT TGTCTCCATC TGGATCCTGT CCTTTATCCT  
 GGCCATTCTT GAAGCGATTG GCTTCGTCAT GGTACCTTTT GAATATAGGG GTGAACAGCA TAAAACTGT ATGCTCAATG  
 CCACATCAAA ATTCATGGAG TTCTACCAAG ATGTAAAGGA CTGGTGGCTC TTCGGGTCTT ATTTCTGTAT GCCCTTGGTG  
 25 TGCATGCGA TCTTCTACAC CCTCATGACT TGTGAGATGT TGAACAGAAG GAATGGCAGC TTGAGAATTG CCTCAGTGA  
 ACATCTTAAG CAGCGTCGAG AAGTGGCAAA AACAGTTTTT TGCTTGGTTG TAATTTTTC TCTTTGCTGG TTCCCTCTTC  
 ATTTAAGCCG TATATTGAAG AAAACTGTGT ATAACGAGAT GGACAAGAAC CGATGTGAAT TACTTAGTTT CTACTGCTC  
 ATGGATTACA TCGGTATTAA CTTGGCAACC ATGAATTCAT GTATAAACC CATAGCTCTG TATTTTGTGA GCAAGAAAT  
 TAAAAATTGT TTCCAGTCAT GCCTCTGCTG CTGCTGTAC CAGTCCAAAA GTCTGATGAC CTCGGTCCCC ATGAACGGAA  
 30 CAAGCATCCA GTGGAAGAAC CACGATCAAA ACAACCACAA CACAGACCGG AGCAGCCATA AGGACAGCAT GAACTGACCA  
 CCCTTAGAAG CACTCCTCGG TACTCCATA ATCCTCTCGG AGAAAAAAT CACAAGGCAA CTGTGAGTCC GGAATCTCT  
 TCTCTGATCC TTCTTCTTA ATTCCTCCC ACACCAAGA AGAAATGCTT TCCAAAACCG CAAGGGTAGA CTGGTTTATC  
 CACCCACAAC ATCTACGAAT CGTACTCTT TAATTGATCT AATTTACATA TTCTGCGTGT TGTATTACG ACTAAAAAT  
 GGTGGGAGCT GGGGAGAAT GAAGACTGTT AAATGAAACC AGAAGGATAT TACTACTTT TGCATGAAAA TAGAGCTTTC  
 35 AAGTACATGG CTAGCTTTTA TGGCAGTTCT GGTGAATGTT CAATGGGAAC TGGTACCAT GAACTTTAG AGATTAACGA  
 CAAGATTTTC TACTTTTTTT AAGTATTTT TTTGCTCTC AGCCAAACAC AATATGGGCT CAAGTCACTT TATTTGAAA  
 TGTCAATTTGG TGCCAGTATC CCGAATTC-3' (FRAG. NO: ) (SEQ ID NO:11851)  
 5'-GAATTCGGGA AAAAGTGAAG GTGTAAGGC AGCACAAGTG CAATAAGAGA TATTTCTCA AATTTGCCTC AAGATGGAAA  
 40 CCCTTTGCCT CAGGGCATCC TTTTGGCTGG CACTGGTTGG ATGTGTAATC AGTGATAATC CTGAGAGATA CAGCACAAT  
 CTAAGCAATC ATGTGGATGA TTACCACT TTTCTGGGCA CAGAGCTCAG CTCTCTGGTT ACCACTCATC AACCCACTAA  
 TTTGGTCTTA CCCAGCAATG GCTCAATGCA CAACTATTGC CCACAGCAGA CTAAAAATTAC TTCAGCTTTC AAATACATTA  
 ACACGTGAT ATCTTGATCT ATTTTCATCG TGGGAATGGT GGGGAATGCA ACTCTGCTCA GGATCATTTA CCAGAACAAA  
 45 TGTATGAGGA ATGGCCCCAA CGCGCTGATA GCCAGTCTTG CCTTGGAGA CCTTATCTAT GTGGTCATTG ATCTCCCTAT  
 CAATGTATTT AAGCTGTCTG CTGGGCGCTG GCCTTTTAT CACAATGACT TTGGCGTATT TCTTTGCAAG CTGTTCCCTC  
 TTTTGCAGAA GTCTCTGGTG GGGATCACCG TCCTCAACCT CTGCGCTCTT AGTGTGACA GGTACAGAGC AGTTGCCTCC  
 TGGAGTCGTG TTAGGGAAT TTGGATTCTT TTGTAACTG CCATTGAAAT TGTCTCCATC TGGATCCTGT CCTTTATCCT  
 GGCCATTCTT GAAGCGATTG GCTTCGTCAT GGTACCTTTT GAATATAGGG GTGAACAGCA TAAAACTGT ATGCTCAATG  
 50 CCACATCAAA ATTCATGGAG TTCTACCAAG ATGTAAAGGA CTGGTGGCTC TTCGGGTCTT ATTTCTGTAT GCCCTTGGTG  
 TGCATGCGA TCTTCTACAC CCTCATGACT TGTGAGATGT TGAACAGAAG GAATGGCAGC TTGAGAATTG CCTCAGTGA  
 ACATCTTAAG CAGCGTCGAG AAGTGGCAAA AACAGTTTTT TGCTTGGTTG TAATTTTTC TCTTTGCTGG TTCCCTCTTC  
 ATTTAAGCCG TATATTGAAG AAAACTGTGT ATAACGAGAT GGACAAGAAC CGATGTGAAT TACTTAGTTT CTACTGCTC  
 ATGGATTACA TCGGTATTAA CTTGGCAACC ATGAATTCAT GTATAAACC CATAGCTCTG TATTTTGTGA GCAAGAAAT  
 TAAAAATTGT TTCCAGTCAT GCCTCTGCTG CTGCTGTAC CAGTCCAAAA GTCTGATGAC CTCGGTCCCC ATGAACGGAA  
 55 CAAGCATCCA GTGGAAGAAC CACGATCAAA ACAACCACAA CACAGACCGG AGCAGCCATA AGGACAGCAT GAACTGACCA  
 CCCTTAGAAG CACTCCTCGG TACTCCATA ATCCTCTCGG AGAAAAAAT CACAAGGCAA CTGTGAGTCC GGAATCTCT  
 TCTCTGATCC TTCTTCTTA ATTCCTCCC ACACCAAGA AGAAATGCTT TCCAAAACCG CAAGGGTAGA CTGGTTTATC  
 CACCCACAAC ATCTACGAAT CGTACTCTT TAATTGATCT AATTTACATA TTCTGCGTGT TGTATTACG ACTAAAAAT  
 GGTGGGAGCT GGGGAGAAT GAAGACTGTT AAATGAAACC AGAAGGATAT TACTACTTT TGCATGAAAA TAGAGCTTTC  
 AAGTACATGG CTAGCTTTTA TGGCAGTTCT GGTGAATGTT CAATGGGAAC TGGTACCAT GAACTTTAG AGATTAACGA  
 60 CAAGATTTTC TACTTTTTTT AAGTATTTT TTTGCTCTC AGCCAAACAC AATATGGGCT CAAGTCACTT TATTTGAAA  
 TGTCAATTTGG TGCCAGTATC CCGAATTC-3' (FRAG. NO: ) (SEQ ID NO:11839)  
 5'-GCCACCATGG AAACCTTTG CCTCAGGGCA TCCTTTTGGC TGGCCTGGT TGGATGTGTA ATCAGTGATA ATCCTGAGAG  
 ATACAGCACA AATCTAAGCA ATCATGTGGA TGAATTCACC ACTTTCTGTG GCACAGAGCT CAGCTTCTCTG GTTACCCTC  
 65 ATCAACCCAC TAATTTGGTC CTACCCAGCA ATGGCTCAAT GCACAACAT TGCACACAGC AGACTAAAA TACTTCAGCT  
 TTCAATATCA TTAACACTGT GATATCTTGT ACTATTTTCA TCGTGGGAAT GGTGGGGAAT GCAACTCTGC TCAGGATCAT  
 TTACCAAGAA CCAATGTATGA GGAATGGGCC CAACGCGCTG ATAGCCAGTC TTGCCCTTGG AGACCTTATC TATGTGGTCA  
 TTGATCTCCC TATCAATGTA TGGCTGGGCG CTGGCCTTTT GATCACAATG ACTTTGGCGT ATTTCTTTGC AAGCTGTTCC  
 CCTTTTGTGA GAAGTCTCG GTGGGGATCA CCTCTCTCAA CCTCTGCGCT CITAGTGTG ACAGGTACAG AGCAGTTGCC  
 TCCTGGAGTC GTGTTCAGGG AATTGGGATT CCTTTGGTAA CTGCCATTGA AATTGCCTCC ATCTGGATCC TGTCTTTAT  
 70 CTTGGCCATT CTTGAAGCGA TTGGCTTCGT CATGGTACC TTTGATATA GGGGTGGACA GCATAAAACC TATGTGGTCA  
 ATGCCACATC AAAATTCATG GAGTCTACC AAGATGTAAA GGAAGTGGT CTCTTCGGGT TCTATTTCTG TATGCCCTTG  
 GTGTGCACTG CGATCTTCTA CACCTCATG ACTGGTGAGA TGTGAAACAG AAGGAATGGC AGCTTGAGAA TTGCCCTCAG  
 TGAACATCTT AAGCAGCGTC GAGAAAGTGG AAAAACAGTT TTTGCTCTGG TTGTAATTTT TGCTCTTTGC TGTCTCCCTC  
 TTAATTTAAG CCGTATATTG AAGAAAACTG TGTATAACGA TGTGGAACAG AACCGATGTG AATTACTTAG TTTCTTACTG  
 75 CTCATGGATT ACATCGGTAT TAACCTGGCA ACCATGAATT CATGTATAAA CCCCATAGCT CTGTATTTTG TGAGCAAGAA

ATTTAAAAAT TGTTTCCAGT CATGCCTCTG CTGCTGCTGT TACCAGTCCA AAAGTCTGAT GACCTCGGTC CCCATGAACG  
GAACAAGCAT CCAGTGAAG AACACGATC AAAACAACCA CAACACAGAC CGGAGCAGCC ATAAGGACAG CATGAAGTGA  
CCACCCCTAG AAGCACTCT-3' (FRAG. NO: ) (SEQ ID NO:12486)

**Substance P Antisense Nucleic Acids and Oligonucleotide Antisense Oligonucleotide Fragments**

- 5 5'-CTGCTGBGGC TTGGGTCTCC GGGCGBTCT CTGCBGBBGB TGCTCBBBGG GCTCCGGCBG TTCCTCCTTG BTCTGGTCGCT  
GTCGTBCCBG TCGGBCCBG BTTCBGBTC BTCBTGGCT CCTBTTCCT CTGCBBCBG CTGBGTGGBG BCBBGBBBB  
BGBCTGCCBB GGCCBCBGG BTTCBTGT TGGBTTCG GBCGBCBGT CCCGCGGGT GCTGAGTTC TCTGGTTCCT  
CCGBGCGCB GTGGTCGCTC CGCGTTCTC TGGTCTCTCC GGTCCGCGG GGTGCTGTCT GGTGCTGTCT GTGGCTTGGG  
TCTCCGGGCG GTTTCCTTCC TTTCCGC-3' (FRAG. NO:1877) (SEQ ID NO:11259)
- 10 5'-CTCC GGGCGB-3' (FRAG. NO:1878) (SEQ ID NO:11260)  
5'-GGCCBCBGG-3' (FRAG. NO:1879) (SEQ ID NO:11261)  
5'-GGGTCTCCGGGCG-3' (FRAG. NO:1880) (SEQ ID NO:11262)  
5'-GGG TCTCCGGGCG G-3' (FRAG. NO:1881) (SEQ ID NO:11263)  
5'-CGTGGTCGCTCCGC-3' (FRAG. NO:1355)(SEQ ID NO:10733)
- 15 5'-GTTTCTCTGGTTCCTCCG-3' (FRAG. NO:1356)(SEQ ID NO:10734)  
5'-GTCCCGCGGGGTGCTG-3' (FRAG. NO:1357)(SEQ ID NO:10735)  
5'-TCTGTGCTGCTCGT-3' (FRAG. NO:1358)(SEQ ID NO:10736)  
5'-GGCTTGGGTCTCCGGGCG-3' (FRAG. NO:1359)(SEQ ID NO:10737)  
5'-GTTTCTCTCTTTTCCGC-3' (FRAG. NO:1360)(SEQ ID NO:10738)
- 20 5'-CTGCTGBGGC TTGGGTCTCC GGGCGBTCT CTGCBGBBGB TGCTCBBBGG GCTCCGGCBG TTCCTCCTTG BTCTGGTCGCT  
GTCGTBCCBG TCGGBCCBG BTTCBGBTC BTCBTGGCT CCTBTTCCT CTGCBBCBG CTGBGTGGBG BCBBGBBBB  
BGBCTGCCBB GGCCBCBGG BTTCBTGT TGGBTTCG GBCGBCBGT CCCGCGGGT GCTGAGTTC TCTGGTTCCT  
CCGBGCGCB-3' (FRAG. NO:1882) (SEQ ID NO:11264)

**Substance P Receptor Nucleic Acids and Antisense Oligonucleotide Fragments**

- 25 5'-GGGCTBBGBT GBTCCBCBTC BCTCCBCGT TGCCCBCCBC BGBGGTCBCC BCBBTGBCCG TGTBGGCBGC TGCCBBBGG  
BCBBTTTGCC BGGCTGGTTG CBCGBBCTGB TTGGGTTCCG BGGTGTBTGT GGBGTGTGT GGGGBBGGT CTGBGTCCBC  
CGGBBGBCG TBTCCBTTC CGBBGTBGG CGGTBBBGGC CTBCTBTCTG TBCBCCBCCC CCTCTGCBG CBGBGTCTG  
TCGTGGCGCC TGGGGCTCBG GGTCCGGGC TAAGATGATC CACATCTA CCACGTTGCC CACCACAGAG GTCACCACAA  
TGACCGTGA GGCAGCTGCC CAAAGGACAA TTGCCAGGC TGGTGCACG AACTGATTGG GTTCCGAGGT GTTAGTGGAG  
30 ATGTTTGGGG AGAGGCTGA GTCCACCGGG AGGACGTTAT CCATTTCGAA GCTAGGCGGT AAAGCCCTAC TATCTGTACA  
CAACCCCT CTGCAGCAGA GTCCTGTCTG GCGCCTGGG GCTCAGGGTC CGTCTGTCTG TGGCGCTGG GGTCTTCTT  
TTGTGGGCTC TTGTGTGGCT GTGGCTGTGG TCTGTGTGT TGTGCTGCTG GGTCTGGGG TGTGGCCTG GGCCTCTCT  
CTGGCTCTC CTGCTGGGCC CCC-3' (FRAG. NO:1883) (SEQ ID NO:11265)  
5'-GGGBGBBGC-3' (FRAG. NO:1884) (SEQ ID NO:11266)
- 35 5'-GGGTC CG-3' (FRAG. NO:1885) (SEQ ID NO:11267)  
5'-GGGCC CCC-3' (FRAG. NO:1886) (SEQ ID NO:11268)  
5'-GTCCTGTCTGGCGCCTGGGGCTC-3' (FRAG. NO:1361)(SEQ ID NO:10739)  
5'-TCTTTTGTGGGCT-3' (FRAG. NO:1362)(SEQ ID NO:10740)  
5'-CTTTGGTGGCTGTGGCTG-3' (FRAG. NO:1363)(SEQ ID NO:10741)
- 40 5'-TGGTCTCTGTGGTTG-3' (FRAG. NO:1364)(SEQ ID NO:10742)  
5'-CTGGCTGGGCTGG-3' (FRAG. NO:1365)(SEQ ID NO:10743)  
5'-GGGTGTGGCCTTGGGGCCGCTCTGGCTCTCTCTGTTGGGCCCC (FRAG. NO:1366)(SEQ ID NO:10744)  
5'-GGGCTAAGAT GATCCACATC ACTACACGT TGCCACCAC AGAGGTCAAC ACAATGACCG TGTAGGCAGC TGCCCAAAGG  
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45 CGGAGGACG TTATCCATTTC GAAGCTAGGC GTAAAGCCC TACTATCTGA CACAACCCCT CTCTGCAGCA GAGTCTGTCT  
GTGGCGCTG GGGCTCAGGTCC-3'(FRAG. NO:1367)(SEQ ID NO:10745)  
5'-GGGCTBBGBT GBTCCBCBTC BCTCCBCGT TGCCCBCCBC BGBGGTCBCC BCBBTGBCCG TGTBGGCBGC TGCCBBBGG  
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GGGBBGBCGT TBTCCBTTC GGBGCTBGG GGTBBBGGCC TCTBTCTGTB CBCBCCCTCT CTCTGCBGCB GBGTCTGTCT  
50 GTGGCGCTG GGGCTCBGG TCC-3' (FRAG. NO:1368) (SEQ ID NO:10746)

**Chymase Antisense Nucleic Acids and Oligonucleotides Antisense Oligonucleotide Fragments**

- 5'-GGBGCTGBTB CTGCBGATTT CBGBGGBBG BBCCCTGBTB CTCBCCBGT TCBGCTCTGG BGCBCBBBG BBBBGBCBGC  
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 ATTGGAGTGG AGTGGAGTGG AATGGAAACT AACAGGAAGA CACTGCACAT GGTAAAGATA AAGATTGTTT CCTGAAACCT  
 TTAATTGTG AGTACATACT CACACATACA TATGTGCTCT CACTGGGACT CTGCAATATG CATTTCTGAC TATGGAACAT  
 15 AGCCATAAAA GTCTTTGCAC TGAACGTICA GTGGGCCTTT CACAAGCTGC CTAATTGGG AAAGAAAAAC ATGGTCCCTC  
 CATTTCTCTG CCCCAACTCC AGAAAAGTCA CCATAGTTGA GGGTACATCT GAGAAGCCAG CACTTGGGAG TTCAGGGGCTC  
 AAGTTCTTTC CTAGAAAAAC ACTGGGTGAT TCTAGGGGAA CTTCCGATCA GAAACAGCCA ATTCAGAGTG AGAGAAGAAA  
 ACGTGACCAT GCAGTTCTCT TGTGTACAG CCTTGCCCTT CTCTGGCTT CTGGGAGTTA TAAAACCCAA GACTGGAAAG  
 GAAACACGAC ATTTGCTCAG GCAGCCTCTC TGGGAAGATG CTGCTTCTTC CTCTCCCTT GCTGCTCTTT CTCTTGTGCT  
 20 CCAGAGCTGA AGCTGGTGAG TATCAGGGTT CTTCCCTCTG AAATCTGCAG TATCAGCTCC TGAACAAAAAG ATGTTTAGTC  
 TGAAATAGCT GACTCCTAAA CAGGTTTCCA AGATCTCTCT TCAAGTGGTCC CACAGAGGAA ATTTCCACTT GGGATGTGTG  
 CCACCCACCC CCACCCCCCA CCCACTGCCA TTCTCTACAG CTTAGGACAC CCCCAGGAAC AAGGAATTTT ACCTCAATTG  
 TAGAAAAGCC CAGAGCAAGT GGAAGGAAAA GGGGTATCCC CAGGAAAAACA GACATGTCTT CTTAATCTTC TGAGCATCAG  
 GGCTACCCAT TACTTTGTGA CTTTCTCACT CTGTGACCAT GCTCAAGAGC TATGGAGAAA TCTAAAAAGC GAACCTGGAC  
 25 AGTGGGTCTT ACACAGAGAC AGAGGAGAGT GGGCCAGGGC AAGGTGGGAG TGGGAGAAAT CTGAGATGAA AACATCAGAA  
 TGGAGCAGAG GCAAGAATGA GATTTCACCT GGGAGGTTAT GGGTGGGGAA AGATACGAAA TACAGGAGAC AGGAGAGGGA  
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 AGAGTATCTA TGGCCGTGTT CAAACCCCTGG GGTGCTCTGT TCCAGGGGAG ATCATCGGGG GCACAGAAATG CAAGCCACAT  
 TCCCGCCCTT ACATGCGCTA CTTGGAAATT GTAACCTCCA ACGGTCCCTC AAAAATTTGT GGTGGTTTCT TTATAAGACG  
 30 GAACTTTGTG CTGACGGCTG CTCATTGTGC AGGAAGGTGA GACAACAGGG TCTATTATC TCCAAATGGG AGATGAACAA  
 CCAGAGTAGC ATCCAGGAAT ACACCTGCAC TGGGGACTGA AGAGGGGGTCT CTGGGTCTTG TCAACTTTCA GGAGAGGGAA  
 GACTTTGGGC TGAAGAGCTT TAGTCTGTGT TTGAATAGTT CCTTGAGCCT CAGTCACTGA GCTAAGCTCC CTTCCGAGGA  
 AAAGGAGGTC CTGTCCGAAG GTCCCTCTTG TTGAGTAGC ACCCTCACC CCTACCCAAC TCAAGACACA CGGCTCACTT  
 TTCAGGGCCC CACCCAGTCT CAGGGCCACT TCCTCTATGG CCTTTTCAAG AACACTGGCT CTAGTTCTCA GGGTCTGAA  
 35 CCCATCATTT TATGGGAGCA GAGAACAGGT CTACATAAGA CCCCCACTTT CCGGTTTTAA CTGATATCTC CTGCTTCAGG  
 GGCTGGCCCT CATGCAGGGT TCCCTGAATT AGGAAGTGTG AACCTGTCTC CCTGAGTCTT CCTGGGCTG TTCAGTCCC  
 AGCAATTCCA GGGGTCTGTAG AAATTGTGTC TGTTCCTGA GAAAGCTCTT TCATGAGTTA AGCCTGAGCC CTCAAATGCC  
 ACAAGTGGCC CATGAAAAGG GAGATGGGTA GAGTCCGGCN ACCCAGTGAC AGAGTTTATG CCTCTTTTCT CAGAATGAGC  
 40 TCACCTCAGA AGAAACCCCA AGCCATCACT GTCCCTCTCT TTTCTTCTCT TCTTCTCTAC AGCAGGTCTA TAACAGTCAC  
 CCTTGGAGCC CATAACATAA CAGAGGAAGA AGACACATGG CAGAAGCTTG AGGTTATAAA GCAATTCCTG CATCCAAACT  
 ATAACACTTC TACTCTTCAC CACGATATCA TGTACTAAA GGTGACAACA CCTCTCTTCT CCCTTTCCAC TTCCCATTTCT  
 CCTAAGCTTC TCCTTCAGGT CCTCATGACC CTGAATTTT CTAGGACTT GGCTATAACA TGAAGCTACT CACCTGTGCC  
 CTCCTGATC ACCTCCAATG GTCCAGAGCC CATTTCGAGG ACTGACAGTC CTTTATTCCC TTCACAGTTG AAGGAGAAAAG  
 45 CCAGCCTGAC CCGGCACTGT GGGACACTCC CCTTCCCAAT CTAATTTCAAC TTTGTCCAC CTGGGAGAAAT GTGCCGGGTG  
 GCTGGCTGGG GAAGAACAGG TGTGTGAAG CCGGGCTCAG AACTCTGCA AGAGGTGAAG CTGAGACTCA TGGATCCCA  
 GGCCTGCAGC CACTTCAGAG ACTTTGACCA CAATCTTCAG CTGTGTGTGG GCAATCCAG GAAGACAAAA TCTGCAITTA  
 AGGTGATCCT CCAACTAGGT TTCCTCTCCA AACTCACTG TTCAGGGACC TGAATGCTCT TAGAAGGAGA TGGGGTCAGC  
 50 AGGTTGTGAG TCAGGTGACA GGGTGAGCAT CACAGGAATT GGTGCTCTCC CGTGGTCCAA GACAGCCTCT GACCATCCAT  
 TCCAGTCTAC TGCATGGGG GCATGGGGTG ACTGTGAGA ATGTGGATGA CGGTCCCAAG AAAGGAAGAA GGGGCATCAG  
 AACTAGATGT ATAAGTGAGG AGCTCCACCT CCTGGGTCTG ACTTTAGGTC TCACTGTGAC TCCAAGCTGG CTGGCAGACA  
 GGAGTGAGT AACTCCCGG CTCACCTTCT TCTCTCTCTC CTCCCTTAC AGGGAGACTC TGGGGGCCCT CTCTGTGTG  
 CTGGGGTGGC CCAGGGCATC GTATCCTATG GACGGTCCGA TGCAAGGCC CCTGCTGTCT TCACCCGAAT CTCCCATTTAC  
 CGGCCCTGGA TCAACAGAT CCTGCAGGCA AATTAATCCT GGATCCTGAG CCAGCCTGAA GGGAAAGCTGG AACTGGACCT  
 TAGCAGCAAA GTGTGTGCAA CTCATTCTGG TTCTACCTT GGTTCCTCA GCCACAACC TAAGCCTCCA AGAGGTCTCC  
 55 TACAGGTAAC AGAACTTCA ATAACTTCA GTGAAGACAC AGCTTCTAGT CGTGAGTGTG TGTCCTCTC TGCTGCTCTC  
 TTCTCTGCA CATGTGACCT GATTCCAGC CCAAGCACCA AGGA-3' (FRAG. NO:) (SEQ ID NO:11836)  
 5'-GGBGCBBCBBG-3' (FRAG. NO:1888) (SEQ ID NO:11270)  
 5'-GGBGCBGC-3' (FRAG. NO:1889) (SEQ ID NO:11271)  
 5'-GGGGCBBCBBG CG-3' (FRAG. NO:1890) (SEQ ID NO:11272)  
 60 5'-CGTTTTCTTCTCTC-3' (FRAG. NO:1369)(SEQ ID NO:10747)  
 5'-GCTGGTTTTCTTTCC-3' (FRAG. NO:1370)(SEQ ID NO:10748)  
 5'-TGGCAGTGGGTGGGGTGGGGTGGGCGC-3' (FRAG. NO:1371)(SEQ ID NO:10749)  
 5'-TTCCTGTTCCTGGGGTGTCT-3' (FRAG. NO:1372)(SEQ ID NO:10750)  
 5'-CTTGCTCTGGGCTTTTCT-3' (FRAG. NO:1373)(SEQ ID NO:10751)  
 65 5'-CCCCTTTCTCTCC-3' (FRAG. NO:1374)(SEQ ID NO:10752) [  
 5'-TGTCTGTTTTCTCTGGG-3' (FRAG. NO:1375)(SEQ ID NO:10753)  
 5'-CTCTCTCTGTCTCTGTGT-3' (FRAG. NO:1376)(SEQ ID NO:10754)  
 5'-CCTTGCCCTGGCCC-3' (FRAG. NO:1377)(SEQ ID NO:10755)  
 5'-TCTTCCCTCTCTGTCTCTGT-3' (FRAG. NO:1378)(SEQ ID NO:10756)  
 70 5'-CCCTGTGTTCCGCCC-3' (FRAG. NO:1379)(SEQ ID NO:10757)  
 5'-GTCTTCCCTCTCTGT-3' (FRAG. NO:1380)(SEQ ID NO:10758)  
 5'-ACCTCTTTTCTCTCCG-3' (FRAG. NO:1381)(SEQ ID NO:10759)  
 5'-CTGGGTGGGGCCCTG-3' (FRAG. NO:1382)(SEQ ID NO:10760)  
 5'-CTGTCTCTGCTCTCC-3' (FRAG. NO:1383)(SEQ ID NO:10761)  
 75 5'-TGGCTTGGGGTTTCTCTG-3' (FRAG. NO:1384)(SEQ ID NO:10762)

5'-TGTCCTCTCTCTCTCTGTT-3' (FRAG. NO:1385)(SEQ ID NO:10763)

5'-GGCTGGCTTCTCTCTCTC-3' (FRAG. NO:1386)(SEQ ID NO:10764)

5'-TTTTGTCTCTCTGGG-3' (FRAG. NO:1387)(SEQ ID NO:10765) [1397]

5'-TGCCCCCTCTCTCTCTTCTTGGG-3' (FRAG. NO:1388)(SEQ ID NO:10766)

5'-TCCTTGGTGCTTGGGCTGGG-3' (FRAG. NO:1389)(SEQ ID NO:10767)

5'-GGBGCTGBTB CTGCBGATTT CBGBGGGGBB BBCCCTGBTB CTCBCCBGCT TCBGCTCTGG BGCBCBBGBG BBBGBGCBGC  
BGGGGGBGBG GBBGBBGBG CBTCTTCCB GBGBGGCTGC CTGBGCBBBT GCTGGTTTC CTTCCBGTG TTGGGTTTB  
TBBCTCCCBG BBGGCBBGBG BGGGGCBBGG-3' (FRAG. NO:1891) (SEQ ID NO:11273)

# Endothelial Nitric Oxide Synthase Nucleic Acids and Antisense Oligonucleotide Fragments

10 5'-GCCTCTTGGG GTGCBGGGCC BTCTCTGCTG CGCTTGGGCG CTGCTGTGCG TCCGTCTGCT GGGGGGCGCG GGTGGCTGGG  
CCCTGTCTGC CGACGACCC CGGGCCGACC CGAGGCTCGG GGGGCTGTGT TCTGGCGCTG GTGGGCTTGG GCGGCTCTGG  
GGGCTGGGTT TCTGTCTGCG CTTGGGCGCT GCGCTCTTGG GGTGCGGGGC GGGGGGCGCG GGGGGGCGCT GTTCGTGGGC  
CTGGGGGTGC CTGTGGCTGC CGGTGCCCC GGTGTGGTGC GCGCTCTGCG TGCCGGTCTG TGGCTGGGTC CCGGCGCGCG  
15 TTCTCTGGG TCCGCGTGGG GTGCTCCGGT TCCTGCTGCT GCTGCTGCGG GCGGCGGTCT TCTTCTTCCG GCGGTGGGTC  
CGCCCCCCT GGCCTTCTGC TCGGGGTCTG GCTGGTGGC GGTGCCCTTG GCGGCGGTCT TCTTCTGCTT GGTCTGGGC  
CGGCGCGGTC TCGGCGTCT CBTGTCTGCT CTTGTGCTGT TCCGGCGGCT CTTCTCTCTT CCGCGCGGCG CCGTCCCGCG  
CGCTCTGTCG CCCTGGCCCG GCGCTCTCTT GCGGCTGTC TCGGGCGGCG GCCTTGGCGC TCCGTTTGGG GCTGCTCTG  
GCGCTTCCCG CCCTCGGCGT GCGGCGCTCT TCCGCGCTGT TGTGCTGGCC CTCGTGGGCC CCTCTCTGCG TCCGCTGTCC  
20 TGTGGTCCCC CGGCTGGTGG CCGGGCCGGT TGGGCGGGCG TGGGCGCGCG CCGGTCTCTC GGGCTGCCCT TCTCCGCGCG  
GGGTCCCGCG CTCTGCTGT TCCCTGGGCT CTTCTGCGCT TCTCTGGGT GGGTGTCTGG TGCCGGGGTC TCCGGGCTTG  
CCCCGCGCTG CTGGGCGTTC TGCGGTCTTG GGTGTGTCTG TGGCCCCGCT CGTGTGCGCC TCCGTGCGCC GTCCGCGGCC  
TCGTCCCTCT CTGGGTGCGC GCGGCGCTGG TCTGGCGCTT TGTCTCTTC CTGGGCGTCT TGGGGTGCBG GCGCCBTCT  
GCTGCGCTG GCGCTGCTG TCGTCCGTC TGTGGGGGG CCGGGTGGC TGGGCGCTGC TTGCCGACG ACCCGGGGCC  
GACCCGAGGC TCGGGGGGCT GTGTCTTGGC GCTGGTGGG TTGGGGCCCT CTGGGGGCTG GGTTCCTG TGCGCTGGG  
25 CCGGCTTGG TGGCGCGTC CTGCTGCCG GCGTGGCTG GGTGCCCGG CCGGTTCTG GGGCTGGG GTGCTGTG TGCGGCTTG  
CCCGGTTGG TGGCGCGTC CTGCTGCCG CCGTGGCTG GGTGCCCGG CCGGTTCTT GGGGTCCG TGGGGTGCTC  
CGGTTCCTG TGCGGCTGCT GCGTGTCTT TCCGGCGGTC GCGGCGTGGT GGTCCGCGCC CCGTGGCTT CTGCTCGGG  
TCTGGCTGTG TGCGGCTGCC CTTGGCGGCG GTCTTCTTCC TGGTGGCTCT GCGGCGGCC GGTCTCGGGC GTCTCGTGT  
30 CCGCTTGTG CTGTTCCGCG CCGTCTTCC TCTTCCGCG CCGGCGCTC CCGGCGGCTC GTGCGCTG GCGGCGCTC  
TCTTGGCGC TGTCTCGGC GCGGCGCTT GCGCTCCGT TGGGGCTGCC TCTGGCGCTT CCGGCGCTG GCGTGGCGC  
TCTTCCCGC CTGTGCTGGT GCGGCTCTG GCGGCTCTT GCGTCCGCT GTCTGTGCT CCGGCGCTG GTGGCGGGC  
CGGTGGGGC GCGTGGGGC CCGGCGGGTC TCCGGGCTG CCCTTCTCCG CCGGGGGTCC CCGGCTCTG CTGTTCCCTG  
GGCTCTTCT CCGTCTCTC GGTGGGTGC TGGTGGCGG GGTGCGCGG GTCTCCCGG CTGCGCGCG GCTGCTGGG GTTCTCGGT  
35 CTGGGGGTG TGTGTGGCC CCGTCTGTC GCGTCCGTC GCGGCTGCG GCGCTCTGCT CCTCTGCT GCGGCGGGC  
CTGGTCTGG CCGTTTGTCT CTTCTGG-3' (FRAG. NO:1892) (SEQ ID NO:11274)  
5'-GCGGGGCGG-3' (FRAG. NO:1893) (SEQ ID NO:11275)  
5'-CGGGGGG-3' (FRAG. NO:1894) (SEQ ID NO:11276)  
5'-GCGGCGCGG-3' (FRAG. NO:1895) (SEQ ID NO:11277)  
5'-CTGTGCGTCCGCTCTGCTGG (FRAG. NO:1390)(SEQ ID NO:10768)  
40 GGGGCGGGGTGGCTGGGCCCTGCTGCCG (FRAG. NO:1391)(SEQ ID NO:10769)  
ACGACCCCGGGCCGACCCGAG (FRAG. NO:1392)(SEQ ID NO:10770)  
GCTCGGGGGGCTGTGTTCTGGCGCTGGTGGG (FRAG. NO:1393)(SEQ ID NO:10771)  
CTTGGGGCCCTCTGGGGGCTGGGTT (FRAG. NO:1394)(SEQ ID NO:10772)  
TCTGTGCGCTGGGCGCTG (FRAG. NO:1395)(SEQ ID NO:10773)  
45 GCGTCTTGGGGTGC (FRAG. NO:1396)(SEQ ID NO:10774)  
GGGCGCGGGGGCGGGGG (FRAG. NO:1397)(SEQ ID NO:10775)  
GCCGCTGTTCTGGGCGCTGGG (FRAG. NO:1398)(SEQ ID NO:10776)  
GCTGCGCTGGGCTGCC (FRAG. NO:1399)(SEQ ID NO:10777)  
GGTTGCCCGGTTGGTGGC (FRAG. NO:1400)(SEQ ID NO:10778)  
50 GCGGCTCTGCTGCCGT (FRAG. NO:1401)(SEQ ID NO:10779)  
CGTTGGCTGGTCCCCCGC (FRAG. NO:1402)(SEQ ID NO:10780)  
CCGTTTCTGGGGTCC (FRAG. NO:1403)(SEQ ID NO:10781)  
GCGTGGGGTGTCTC (FRAG. NO:1404)(SEQ ID NO:10782)  
GGTCTCTGTCGCG (FRAG. NO:1405)(SEQ ID NO:10783)  
55 CTGCTGCGCTGTCTTCC (FRAG. NO:1406)(SEQ ID NO:10784)  
GGCGGTGGCGGCTGGTGGTCC (FRAG. NO:1407)(SEQ ID NO:10785)  
GCCCCCCTGGCCTTCTGCTC (FRAG. NO:1408)(SEQ ID NO:10786)  
GGGGTCTGGCTGGT (FRAG. NO:1409)(SEQ ID NO:10787)  
TGCCGGTGGCCTTGGCGGC (FRAG. NO:1410)(SEQ ID NO:10788)  
60 GGTCTTCTCTGGTG (FRAG. NO:1411)(SEQ ID NO:10789)  
GCTTGGGCGCGCGGCTCTCGG (FRAG. NO:1412)(SEQ ID NO:10790)  
GCGTCTGCTGTTCCG (FRAG. NO:1413)(SEQ ID NO:10791)  
CTCTGTGCTGTCCGCGC (FRAG. NO:1414)(SEQ ID NO:10792)  
CTCCTTCTCTTCCGCGC (FRAG. NO:1415)(SEQ ID NO:10793)  
65 GCGGCTTCCGCGC (FRAG. NO:1416)(SEQ ID NO:10794)  
GCTGCTGCGGCTGGCC (FRAG. NO:1417)(SEQ ID NO:10795)  
GGCCTCTCTGCGCGC (FRAG. NO:1418)(SEQ ID NO:10796)  
TGTCTCGGCGCGGCGCTTGGC (FRAG. NO:1419)(SEQ ID NO:10797)  
GCTCCGTTTGGGGCTG (FRAG. NO:1420)(SEQ ID NO:10798)  
70 CCGTGGCGCTTCC (FRAG. NO:1421)(SEQ ID NO:10799)  
GGCCTCGGCGGCGGCTC (FRAG. NO:1422)(SEQ ID NO:10800)  
TCTTCCGCTGTGC (FRAG. NO:1423)(SEQ ID NO:10801)  
TGGTGGCGCTGTG (FRAG. NO:1424)(SEQ ID NO:10802)  
GCGGCTCTGGCGCTCCGCTGTCC (FRAG. NO:1425)(SEQ ID NO:10803)  
75 TGTGGTCCCCGCGCTGGT (FRAG. NO:1426)(SEQ ID NO:10804)

- GGCCGGGCCGGTTGGGCGGGC (FRAG. NO:1427)(SEQ ID NO:10805)  
 GTGGGCGCCGGCGGTCCTCC (FRAG. NO:1428)(SEQ ID NO:10806)  
 GGGCTGCCCTTCTCC (FRAG. NO:1429)(SEQ ID NO:10807)  
 GCCGGGGGTCCCGC (FRAG. NO:1430)(SEQ ID NO:10808)  
 5 GCTCCTGCTGTTCCCTGGGCTCTTCTGCC (FRAG. NO:1431)(SEQ ID NO:10809)  
 TCTCTCCTGGGTGGGTGCTGGGTGCCG (FRAG. NO:1432)(SEQ ID NO:10810)  
 GGGTCTCCGGGCTTG (FRAG. NO:1433)(SEQ ID NO:10811)  
 CCCCgcgctgctgggCGTTCTGC (FRAG. NO:1434)(SEQ ID NO:10812)  
 GGTTCTGGGGTTGTC (FRAG. NO:1435)(SEQ ID NO:10813)  
 10 TGTGGCCCCGCTCG (FRAG. NO:1436)(SEQ ID NO:10814)  
 TGTGCCCTCCGTCGCC (FRAG. NO:1437)(SEQ ID NO:10815)  
 CGTCGCCGCTCGTCC (FRAG. NO:1438)(SEQ ID NO:10816)  
 CCTCTGGGTGCGC (FRAG. NO:1439)(SEQ ID NO:10817)  
 GCGGGCTGGTCT (FRAG. NO:1440)(SEQ ID NO:10818)  
 15 GGCGTTTGTCTCTTCTG (FRAG. NO:1441)(SEQ ID NO:10819)  
 5'-GCGTCTTGGGTGCBGGGCCBCTCTGCTGCGCTGGGCGCTG-3'(FRAG. NO:1896) (SEQ ID NO:11278)

# Inducible Nitric Oxide Synthase Nucleic Acids and Antisense Oligonucleotide Fragments

- 5'-CTGCCCCBGT TTTTGTCTC CBCBTGCCGT GGGGBGGBCB BTGGCTGCCT CCCCggggTT TCTGCTGCTT GCTGCTCTT  
 TCCCGTCTCC CTCTTTTCCC GTCTCTTTT TGCCTCTTTG GGTTCCTGTT GTTCTGGCC TGCTTGGTGG CGGCTTGTGC  
 20 GTTCTCTCTC TCTCTCTTG GGTCTCCGCT TCTCGTCTG CTTTTCTCTG TCTCTGTCG GCCGTTCCTC CTCCGGCGTC  
 CTCCTGCCCT GTGCTGTTT CCTCGGGTGG TGCGGGTCCC GGTGCTCCCC CGGCGGGCCG GCTGGTTGCC TGGGCTGTG  
 TGGTGGGGTG TGGGGCCGCT GGGTTGGGG TGTTGGTGGG TCTCTGTGG CCTGTGGGGC TGTGTGTGTC TCTGTGGCG  
 TGTGCTGGGT CTTGGGGCTT CCTCCCTTGT GCTGGGTGCG GCCTCCCCGC CCCCCTTCTG GGCGGTGGC CTGGCTCCTT  
 GTGGGCGCTT CTGGCTCTG CCTGTCTT CTTGCGCTCG TGGTGTCTG GCTGC CATATGTATG GGAATACTGT  
 25 ATTTGAGGCA TTATAAGGAA TGAAATTATA GGCCGGGCAT TGTGGCTAAC CCTTGTAATC CTAGCACTTT GAGAGGCTGA  
 AGTGGGCGAG TCACTTGAGC TTCAGAGTTC GAGACCAGCA TGGACAACAT GGTGAAACCC AGTCTCTACC AAAAACACAA  
 AAATATTAGC TGGGTGTGGT GGTGCATGCC TGTAGTCCCA GCTACTCAGG AGGCTGAGGT GGGAGGATCG CTTGAGCCTG  
 GGAGGCAGAA GTTGCAATGA GCAGAGATCG TGCCACTCCG CTCAGTCTT GGTGACAGAA TGAGACTCCA TCTCAAAAT  
 AAATAAATAA ATAAATAAAA TAAATGAAAT GAAATTATAA GAAATTACCA CTTTTTCATG TAAGAAGTGA TCATTTCAT  
 30 TATAAGGGAA GGAATTAAAT CCTACCTGCC ATTCCACCAA AGCTTACCTA GTGCTAAAGG ATGAGGTGTT AGTAAGACCA  
 ACATCTCAGA GGCCTCTCTG TGCCAATAGC CTCTCTCTCT TCCCTTCCA AAAACCTCAA GTGACTAGTT CAGAGGCTG  
 TCTGGAATAA TGGCATCATC TAATATCACT GGCTTCTGAG AACCTGGGCA TTTTCCAGTG TGTTCATAC TGTCATATT  
 CCCCAGCACT CCTGGACTCC TGTACAAGC TGGAAAAGTG AGAGGATGGA CAGGGATTAA CCAGAGAGCT CCTGTCTGAG  
 GAAAAAATCT CCCAGATGCT GAAAGTGAGG CCATGTGGCT TGGCCAAATA AAACCTGGCT CCGTGGTGCC TCTGTCTTAG  
 35 CAGCCACCCT GCTGATGAAC TGCCACCTTG GACTTGGGAC CAGAAAGAGG TGGGTGGGT GAAGAGGCAC CACACAGAGT  
 GATGTAACCA CAAGATCAGG TCACCCACAG GCCCTGGGAC TCACAGTCAT AAATTAGCTA ACTGTACACA AGCTGGGAC  
 ACTCCCTTGG GAAACCAAAA AAAAAAAGAG CTTTATGCA AAAACAACCTC TCTGGATGGC ATGGGGTGAG  
 TATAAATACT TCTTGGCTGC CAGTGTGTTT ATAACCTTGT AGCGAGTCGA AAAGTGGGCT TCCGGCCGCA GAGAAGTCA  
 CCTCATCTCT GCTTAAAAAT CTCTCGGCA CTTTGTATGA GGGGACTGGG CAGTTCTAGA CAGTCCCGAA GTTCTCAAGG  
 40 CACAGGTCTC TTTCTGTTT GACTGTCTT ACCCGGGGA GGCAGTGCA CCAGCTGCAA GGTGAGTTGC C CATATGTATG  
 GGAATACTGT ATTTGAGGCA TTATAAGGAA TGAAATTATA GGCCGGGCAT TGTGGCTAAC CTTGTAATC CTAGCACTTT  
 GAGAGGCTGA AGTGGGCGAG TCACTTGAGC TTCAGAGTTC GAGACCAGCA TGGACAACAT GGTGAAACCC AGTCTCTACC  
 AAAAACACAA AAATATTAGC TGGGTGTGGT GGTGCATGCC TGTAGTCCCA GCTACTCAGG AGGCTGAGGT GGGAGGATCG  
 CTTGAGCCTG GGAGGCAGAA GTTGCAATGA GCAGAGATCG TGCCACTCCG CTCAGTCTT GGTGACAGAA TGAGACTCCA  
 45 TCTCAAAAT AAATAAATAA ATAAATAAAA TAAATGAAAT GAAATTATAA GAAATTACCA CTTTTTCATG TAAGAAGTGA  
 TCATTTCAT TATAAGGGAA GGAATTAAAT CCTACCTGCC ATTCCACCAA AGCTTACCTA GTGCTAAAGG ATGAGGTGTT  
 AGTAAGACCA ACATCTCAGA GGCCTCTCTG TGCCAATAGC GTTCTCTCT TTTCCCTTCCA AAAACCTCAA GTGACTAGTT  
 CAGAGGCTGA TCTGGAATAA TGGCATCATC TAATATCACT CTTCTCTGAG AACCTGGGCA TTTTCCAGTG TGTTCATAC  
 TGTCAATATT CCCCAGCTT CCTGGACTCC TGTACAAGC TGGAAAAGTG AGAGGATGGA CAGGGATTAA CCAGAGAGCT  
 50 CCTGTCTGAG GAAAAAATCT CCCAGATGCT GAAAGTGAGG CCATGTGGCT TGGCCAAATA AAACCTGGCT CCGTGGTGCC  
 TCTGTCTTAG CAGCCACCCT GCTGATGAAC TGCCACCTTG GACTTGGGAC CAGAAAGAGG TGGGTGGGT GAAGAGGCAC  
 CACACAGAGT GATGTAACAG CAAGATCAGG TCACCCACAG GCCCTGGGAC TCACAGTCAT AAATTAGCTA ACTGTACACA  
 AGCTGGGAC ACTCCCTTGG GAAACCAAAA AAAAAAAGAG CTTTATGCA AAAACAACCTC TCTGGATGGC ACTGTACACA  
 ATGGGGTGAG TATAAATACT TCTTGGCTGC CAGTGTGTTT ATAACCTTGT AGCGAGTCGA AAAGTGGGCT TCCGGCCGCA  
 55 GAGAAGTCA CACTATTCTT GCTTAAAAAT CTCTCGGCA CTTTGTATGA GGGGACTGGG CAGTTCTAGA CAGTCCCGAA  
 GTTCTCAAGG CACAGGTCTT TCTGTGTTT GACTGTCTT ACCCGGGGA GGCAGTGCA CCAGCTGCAA GGTGAGTTGC C-3'  
 (FRAG. NO: ) (SEQ ID NO:12385)  
 5'-CTGCTTTAAA ATCTCTCGC CACCTTTGAT GAGGGGAGTG GGCAGTTCTA GACAGTCCCG AAGTTCTCAA GGCACAGGTC  
 TCTTCTGGT TTGACTGTCC TTACCCGGG GAGGCAGTGC AGCCAGTGC AAGCCCCACA GTGAAGAACA TCTGAGCTCA  
 60 AATCCAGATA AGTGACATAA GTGACCTGCT TTGTAAAGCC ATAGAGATGG CCTGTCTCTG GAAATTTCTG TTCAAGACCA  
 AATTCCACCA GTATGCAATG AATGGGAAA AAGACATCAA CAACAATGTG GAGAAAGCCC CCTGTGCCAC CTCCAGTCCA  
 GTGACACAGG ATGACCTTCA GTATCACAAC CTCAGCAAGC AGCAATGA GTCCCCGAG CCCCTCGTGG AGACGGGAAA  
 GAAAGTCTCCA GAATCTCTGG TCAAGCTGGA TGCAAGCCCA TGTCTCTCC CACGGCATGT GAGGATCAAA AACTGGGGCA  
 GCGGGATGAC TTTCCAAGAC ACACCTTACC ATAAGGCCAA AGGGATTITA ACTTGCAGGT CCAATCTTGG CCTGGGGTCC  
 65 ATTATGACTC CCAAAAGTTT GACCAGAGGA CCCAGGGACA AGCCTACCCC TCCAGATGAG CTCTACCTC AAGCTATOGA  
 ATTTGTCAAC CAATATTACG GCTCCTTCAA AGAGGCAAAA ATAGAGGAAC ATCTGGCCAG GGTGGAAGCG GTAACAAAGG  
 AGATAGAAAC AACAGGAACC TACCAACTGA CCGAGATGTA GCTCTCTT GCCACCAAGC AGGCTGTGCG AACTGGCCCA  
 CGCTGCATTG GGAGGATCCA GTGGTCCAAC CTGCAGGTCT TCGATGCCCG CAGCTGTTCC ACTGCCCCGG AAATGTTTGA  
 ACACATCTGC AGACACGTGC GTTACTCCAC CAACAATGCG AACATCAGT CCGCCATCAC CGTGTCCCC CAGCGGAGTG  
 70 ATGGCAAGCA GCACTTCCGG GTGTGGAATG CTCAGCTCAT CCGCTATGCT GGCTACCAGA TGCCAGATGG CAGCATCAGA  
 GGGGACCCTG CCAACGTGGA ATTACTCAG CTGTGCTACG ACCGTGGGCT GAAGGCCAAG TACGGCCGCT TCGATGTGGT  
 CCCCCTGGTC CTGCAGGCCA ATGGCCGTGA CCCTGAGCTC TTGAAATCC CACCTGACCT TGTGCTTGA GTGGCCATGG  
 AACATCCCAA ATACGAGTGG TTTCGGGAAC TGGAGCTAAA GTGTACGCC CTGCTGTCAG TGGCCAAAT GCTGCTTGA  
 GTGGGCGGCC TGGAGTTCCC AGGGTGCCCC TTCAATGGCT GTGATACGG CACAGAGATC GGAGTCCGGG ACTTCTGTGA  
 75 CGTCCAGCGC TACAACATCC TGGAGGAAGT GGGCAGGAGA ATGGCCCTGG AAACGCACAA GCTGGCCTCG CTCTGAAAG

ACCAGGCTGT CGTTGAGATC AACATTGCTG TGATCCATAG TTTTCAGAAG CAGAATGTGA CCATCATGGA CCACCACTCG  
 GCTGCAGAAT CCTTCATGAA GTACATGCAG AATGAATACC GGTCCCCTGG GGGCTGCCCG GCAGACTGGA TTTGGCTGGT  
 CCTCCCATG TCTGGGAGCA TCACCCCGCT GTTTTACCAG GAGATGCTGA ACTACGTCCT GTCCCTTTTC TACTACTATC  
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AGTTCGGGGA GAGCGGCTGC CCGACTCAGG TCCGCCCCG CAGGATCAGC CCCGCTCTC CCCTCTTGAG GTGGTGCCTT  
CTCATCTCTG TCCAGAGGCT GCAAGGATTC AGCATTATTC CTCCAGGAAG GAGCAAAACG CCTCTTTTCC CTCTCTAGGC  
CTGTTGCCCT GGGCCTGGGT CCGCCTTAAT CTGGAAGGCC CCTCCAGCA GCGGTACCCC AGGGCCTACT GCCACCCGCT  
55 TCTGTTTCT TACTCCGAAT GTTAGATTCC TCTTGCTCT CTAGGAGTA TCTTACCTGT AAAGTCTAAT CTCTAATCA  
AGTATTTATT ATTGAAGATT TACCATAAGG GACTGTGCCA GATGTTAGGA GAACTACTAA AGTGCTTACC CCAGCTC-3' (FRAG.  
NO:)(SEQ ID NO:11877)  
5'-CCCCGGGG-3' (FRAG. NO:1898) (SEQ ID NO:11280)  
5'-GGGGCCGCTGGG-3' (FRAG. NO:1899) (SEQ ID NO:11281)  
60 5'-GGGGGTGTGG-3' (FRAG. NO:1900) (SEQ ID NO:11282)  
5'-CTGCTCCCCGGGGT-3' (FRAG. NO:1442) (SEQ ID NO:10820)  
5'-TTCTGCTGCTTGTG-3' (FRAG. NO:1443) (SEQ ID NO:10821)  
5'-CTTCTTTCCGCTCTCC-3' (FRAG. NO:1444) (SEQ ID NO:10822)  
5'-CTTCTTTCCGCTCTCC-3' (FRAG. NO:1445) (SEQ ID NO:10823)  
65 5'-TTTTCCTCTTTG-3' (FRAG. NO:1446) (SEQ ID NO:10824)  
5'-GGTTCCTGTGTTTCT-3' (FRAG. NO:1447) (SEQ ID NO:10825)  
5'-GGCCTGCTTGGTGGCG-3' (FRAG. NO:1448) (SEQ ID NO:10826)  
5'-GCTTGTGCGTTCC-3' (FRAG. NO:1449) (SEQ ID NO:10827)  
5'-TCTCTTCTCTTGGGTCTCCGCTCTCGTCTGCC-3' (FRAG. NO:1450) (SEQ ID NO:10828)  
70 5'-TTTTCCTGCTCTGTCGC-3' (FRAG. NO:1451) (SEQ ID NO:10829)  
5'-GCCGTTCCTCTCC-3' (FRAG. NO:1452) (SEQ ID NO:10830)  
5'-GGCGTCTCTGCCC-3' (FRAG. NO:1453) (SEQ ID NO:10831)  
5'-TGCTGCTTTGCTCCG-3' (FRAG. NO:1454) (SEQ ID NO:10832)  
5'-GTGGTGGGGTCCC-3' (FRAG. NO:1455) (SEQ ID NO:10833)  
75 5'-GGTGTCTCCCCGGC-3' (FRAG. NO:1456) (SEQ ID NO:10834)



- 5'-GGGCCGGCTGGTTGCCCTGGGC-3' (FRAG. NO:1457)(SEQ ID NO:10835)  
 5'-CTGTCTGGTGGGGGTGGGGCC-3' (FRAG. NO:1458)(SEQ ID NO:10836)  
 5'-GCTGGGTTGGGGGTGGGTG-3' (FRAG. NO:1459)(SEQ ID NO:10837)  
 5'-GGCTCTTCTGTGGCC-3' (FRAG. NO:1460)(SEQ ID NO:10838)  
 5'-TGTGGGGCTGTTGGTG-3' (FRAG. NO:1461)(SEQ ID NO:10839)  
 5'-TCTCTGTGGGCGTGTG-3' (FRAG. NO:1462)(SEQ ID NO:10840)  
 5'-CTGGGTCTGGGGCTTC-3' (FRAG. NO:1463)(SEQ ID NO:10841)  
 5'-CTCCCTTGTGCTGGG-3' (FRAG. NO:1464)(SEQ ID NO:10842)  
 5'-TGCGGCTCCCCGC-3' (FRAG. NO:1465)(SEQ ID NO:10843)  
 5'-CCCCCTTCTGGGCC-3' (FRAG. NO:1466)(SEQ ID NO:10844)  
 5'-GGTGGCCTGGCTCCTTGTGG-3' (FRAG. NO:1467)(SEQ ID NO:10845)  
 5'-GCGCTTCTGGCTCTGTG-3' (FRAG. NO:1468)(SEQ ID NO:10846)  
 5'-CCCTGTCTTCTTCGCCTCGT-3' (FRAG. NO:1469)(SEQ ID NO:10847)  
 5'-GGCTGTGGGCTGC-3' (FRAG. NO:1470)(SEQ ID NO:10848)  
 5'-CTGCCCBGTTTTTGTBCTCCTBCBTGCCGTGGGBGGBCBTGG-3' (FRAG. NO:1901) (SEQ ID NO:11283)

#### **NE-κB Nucleic Acids and Antisense Oligonucleotide Fragments**

- 5'-CGGCCCTTCT CACTGGAGGC ACCGGGACGT CCTCCATGGG AGGGTTGGGC TTGGCCGGGG CTGCCCGGTG CCTCCTCTTG  
 GCTGGTCCCT CGTTGTCTT GGGCCCCG TCCCGCTGCT CGGCCCTCGT GTTCTTTGGC CTCCTGTGTC GCCTGTGTC  
 TTGTCCCGTC CCCTCTCGC TTGCGTTTCC CTCTTCCCTG TCTTCCAGGC CTCCTCCGC TTCCGCTGCT GGGGCCCGCG  
 20 CCGGGGGGGC GCTCGGCTCC GCGGCTTCT CCCCAGGCTGG GGGTCTCTGG TCTCCGGGGC CTGCGGCTCG CGGGCTCGGG  
 GTCGCGTGG CCGCGCGCG CGTCCGCGGT GGGTGGCGCT GTCCCGCGT GGTGTGTCTC CGTTCCTGTC CTGCGCCGTC  
 CTGTGTGCC CGTGGGTCC TGGCGTGGT GGGGGCGTC TGGTGCCTCG TCTGCCCGT GGGGCTTCGG GCTCGGGCT  
 GTTCGTCCCC CCGCGGCTC TGTGGCTCC GGGGCTCTC GTTTCGCTG CTTCGGGTGT CCTTCTCGGC GTGTGGCCCC  
 GGGTCCCGGC CTGTGGGC TGGCGGGGT CGCTGCCCTG GGCTTCTGGC CCGTCTGGT GTCTGTGGT GCTGTGTCTG  
 25 GGTGTGTG CTCTGTGCTG GCGCTTCTC TGCCTCTGC TCCGCCCTCC TGGTGGCTCG GCTGGGGGTG CCCGTGCGGG  
 5'-GGGCGGGGTCCG-3' (FRAG. NO:1903) (SEQ ID NO:11285)  
 5'-GCGCCGTCC-3' (FRAG. NO:1904) (SEQ ID NO:11286)  
 5'-GGGCGTGGTGG-3' (FRAG. NO:1905) (SEQ ID NO:11287)  
 5'-GTTGGGCTTGGCCGGGG-3' (FRAG. NO:1471)(SEQ ID NO:10849)  
 5'-CTGCCCGGTGCTCC-3' (FRAG. NO:1472)(SEQ ID NO:10850)  
 5'-TCTTGGCTGTCCCTCGT-3' (FRAG. NO:1473)(SEQ ID NO:10851)  
 5'-TGCTCTTGGCCCC-3' (FRAG. NO:1474)(SEQ ID NO:10852)  
 5'-GCTCCCGCTGCTCGGCTCCGT-3' (FRAG. NO:1475)(SEQ ID NO:10853)  
 5'-GTTCTTGGCTCTGTCTCC-3' (FRAG. NO:1476)(SEQ ID NO:10854)  
 5'-GCCTGTGTCTTGTCC-3' (FRAG. NO:1477)(SEQ ID NO:10855)  
 5'-CGTCCCTCTCGCTTGCCTTTC-3' (FRAG. NO:1478)(SEQ ID NO:10856)  
 5'-CCTCTTCTGTCTTCCA-3' (FRAG. NO:1479)(SEQ ID NO:10857)  
 5'-GGCCTTCTCCGCTTCCGCTGC-3' (FRAG. NO:1480)(SEQ ID NO:10858)  
 5'-TGGGGCCCGCGCCGG-3' (FRAG. NO:1481)(SEQ ID NO:10859)  
 5'-GGGGGCGCTCGGCTCCGCGCTTCTCCCGG-3' (FRAG. NO:1482)(SEQ ID NO:10860)  
 5'-CTGGGGGTCTGG-3' (FRAG. NO:1483)(SEQ ID NO:10861)  
 5'-TCTCCGGGGCTGCGGCTCGC-3' (FRAG. NO:1484)(SEQ ID NO:10862)  
 5'-GGGCTCGGGGCTGCGTGC-3' (FRAG. NO:1485)(SEQ ID NO:10863)  
 45 5'-GCGCGCGGCTCGGCTCCGCGTG-3' (FRAG. NO:1486)(SEQ ID NO:10864)  
 5'-GGTGGCGCTGCCCCGC-3' (FRAG. NO:1487)(SEQ ID NO:10865)  
 5'-GTGGTGTGTCTCCGTCTCGTCTGCGCCGTG-3' (FRAG. NO:1488)(SEQ ID NO:10866)  
 5'-CTGGTCTGCGCGTG-3' (FRAG. NO:1489)(SEQ ID NO:10867)  
 5'-GTCCTGGGCGTGGTG-3' (FRAG. NO:1490)(SEQ ID NO:10868)  
 5'-GGGGCGTCTGGTG-3' (FRAG. NO:1491)(SEQ ID NO:10869)  
 5'-CTCGTCTGCCCCGTG-3' (FRAG. NO:1492)(SEQ ID NO:10870)  
 5'-GGGCTTGGGGCTCGG-3' (FRAG. NO:1493)(SEQ ID NO:10871)  
 5'-GGCTGTCTGCCCCCTGCGCTCTGTGGCCTCC-3' (FRAG. NO:1494)(SEQ ID NO:10872)  
 5'-GGGGCTCTCGTTTC-3' (FRAG. NO:1495)(SEQ ID NO:10873)  
 5'-GCTGCTTGGGTGCTCTTC-3' (FRAG. NO:1496)(SEQ ID NO:10874)  
 5'-GCGCTGTGGCCCCGG-3' (FRAG. NO:1497)(SEQ ID NO:10875)  
 5'-GTCCCGGCTGCTGGGCTGGCGGGGTC-3' (FRAG. NO:1498)(SEQ ID NO:10876)  
 5'-GCTGCCCTGGGCTTCTGGCCGTCT-3' (FRAG. NO:1499)(SEQ ID NO:10877)  
 5'-GGTTGTCTGCTGGT-3' (FRAG. NO:1500)(SEQ ID NO:10878)  
 60 5'-GCTTGTCTCGGTTCTGG-3' (FRAG. NO:1501)(SEQ ID NO:10879)  
 5'-CCTCTGTGCTGGG-3' (FRAG. NO:1502)(SEQ ID NO:10880)  
 5'-GCTTCTGCTCTCTGCTCC-3' (FRAG. NO:1503)(SEQ ID NO:10881)  
 5'-GCCCTCTGTGGCTC-3' (FRAG. NO:1504)(SEQ ID NO:10882)  
 5'-GGCTGGGGGTGCGGCTGCG-3' (FRAG. NO:1505)(SEQ ID NO:10883)  
 5'-GGGGTGGGTGTGGGTGT-3' (FRAG. NO:1506)(SEQ ID NO:10884)  
 65 5'-TTCGGGGTCTCCCCCTCC-3' (FRAG. NO:1507)(SEQ ID NO:10885)  
 5'-CGGCCCTCTCACTGAGGCACCGGCAGTCTCCATGGGAGG-3' (FRAG. NO:1906)(SEQ ID NO:11288)

#### **Human Major Basic Protein Nucleic Acids and Antisense Oligonucleotide Fragments**

- 5'-GTT TCA TCT TGG CTT TAT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC TCC CCT GCC  
 70 GTG TTG TCT GTG GGT GTC GTT TCG CTC TTG TTG CCC TGG GCC CTT CCC TGC TGG GGG GGA GTT TCA TCT TGG GTT TCB  
 TCT TGG CTT TBT CCCTC CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC TCC CCT GCC GTG TTG  
 TCT GTG GGT GTC GTT TCG CTC TTG CCC TGG GCC CTT CCC TGC TGG GGG GGB GTT TCB TCT TGG-3' (FRAG. ID:1907)  
 (SEQ ID NO:11289)  
 5'-GGG GGA GTT-3' (FRAG. ID:1908) (SEQ ID NO:11290)

- 5'-G CCC TGG GCC C-3' (FRAG. ID:1909) (SEQ ID NO:11291)  
 5'-GTT TCA TCT TGG CTT TAT CC-3' (FRAG. NO:1508) (SEQ ID NO:10886)  
 5'-TCT CCC CTT GTT CCT CCC C-3' (FRAG. NO:1509) (SEQ ID NO:10887)  
 5'-TCT CCT GCT CTG GRG TCT CCT C-3' (FRAG. NO:1510) (SEQ ID NO:10888)  
 5 5'-TTC CCT CCC TCC CCT GCC-3' (FRAG. NO:1511) (SEQ ID NO:10889)  
 5'-GTG TTG TCT GTG GGT GTC C-3' (FRAG. NO:1512) (SEQ ID NO:10890)  
 5'-GTT TCG CTC TTG TTG CCC-3' (FRAG. NO:1513) (SEQ ID NO:10891)  
 5'-TGG GCC CTT CCC TGC TGG-3' (FRAG. NO:1514) (SEQ ID NO:10892)  
 5'-GGG GGA GTT TCA TCT TGG-3' (FRAG. NO:1515) (SEQ ID NO:10893)  
 10 5'-GTT TCA TCT TGG CTT TAT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC TCC CCT GCC  
 GTG TTG TCT GTG GGT GTC GTT TCG CTC TTG TTG CCC TGG GCC CTT CCC TGC TGG GGG GGA GTT TCA TCT TGG-3' (FRAG.  
 ID:1910) (SEQ ID NO:11292)  
 5'-GTT TCB TCT TGG CTT TBT CCTCT CCC CTT GTT CCT CCC CTCT CCT GCT CTG GRG TCT CCT C TTC CCT CCC TCC CCT GCC  
 GTG TTG TCT GTG GGT GTC GTT TCG CTC TTG TTG CCC TGG GCC CTT CCC TGC TGG GGG GGB GTT TCB TCT TGG-3' (FRAG.  
 15 ID:1911) (SEQ ID NO:11293)

#### **Human Eosinophil Major Basic Protein Nucleic Acids and Antisense Oligonucleotide Fragments**

- 5'-GGG GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1516) (SEQ ID NO:10894)  
 5'-GGG GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1517) (SEQ ID NO:10895)  
 5'-GGG GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1518) (SEQ ID NO:10896)  
 20 5'-GGG GGB GTT TCB TCT TGG C-3' (FRAG. NO:1519) (SEQ ID NO:10897)  
 5'-GGG GGB GTT TCB TCT TGG-3' (FRAG. NO:1520) (SEQ ID NO:10898)  
 5'-GGG GGB GTT TCB TCT TG-3' (FRAG. NO:1521) (SEQ ID NO:10899)  
 5'-GGG GGB GTT TCB TCT T-3' (FRAG. NO:1522) (SEQ ID NO:10900)  
 5'-GGG GGB GTT TCB TCT-3' (FRAG. NO:1523) (SEQ ID NO:10901)  
 25 5'-GGG GGB GTT TCB TC-3' (FRAG. NO:1524) (SEQ ID NO:10902)  
 5'-GGG GGB GTT TCB T-3' (FRAG. NO:1525) (SEQ ID NO:10903)  
 5'-GGG GGB GTT TCB-3' (FRAG. NO:1526) (SEQ ID NO:10904)  
 5'-GG GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1527) (SEQ ID NO:10905)  
 5'-GG GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1528) (SEQ ID NO:10906)  
 30 5'-GG GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1529) (SEQ ID NO:10907)  
 5'-GG GGB GTT TCB TCT TGG C-3' (FRAG. NO:1530) (SEQ ID NO:10908)  
 5'-GG GGB GTT TCB TCT TGG-3' (FRAG. NO:1531) (SEQ ID NO:10909)  
 5'-GG GGB GTT TCB TCT TG-3' (FRAG. NO:1532) (SEQ ID NO:10910)  
 5'-GG GGB GTT TCB TCT T-3' (FRAG. NO:1533) (SEQ ID NO:10911)  
 35 5'-GG GGB GTT TCB TCT-3' (FRAG. NO:1534) (SEQ ID NO:10912)  
 5'-GG GGB GTT TCB TC-3' (FRAG. NO:1535) (SEQ ID NO:10913)  
 5'-GG GGB GTT TCB T-3' (FRAG. NO:1536) (SEQ ID NO:10914)  
 5'-G GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1537) (SEQ ID NO:10915)  
 5'-G GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1538) (SEQ ID NO:10916)  
 40 5'-G GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1539) (SEQ ID NO:10917)  
 5'-G GGB GTT TCB TCT TGG C-3' (FRAG. NO:1540) (SEQ ID NO:10918)  
 5'-G GGB GTT TCB TCT TGG-3' (FRAG. NO:1541) (SEQ ID NO:10919)  
 5'-G GGB GTT TCB TCT TG-3' (FRAG. NO:1542) (SEQ ID NO:10920)  
 5'-G GGB GTT TCB TCT T-3' (FRAG. NO:1543) (SEQ ID NO:10921)  
 45 5'-G GGB GTT TCB TCT-3' (FRAG. NO:1544) (SEQ ID NO:10922)  
 5'-G GGB GTT TCB TC-3' (FRAG. NO:1545) (SEQ ID NO:10923)  
 5'-GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1546) (SEQ ID NO:10924)  
 5'-GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1547) (SEQ ID NO:10925)  
 5'-GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1548) (SEQ ID NO:10926)  
 50 5'-GGB GTT TCB TCT TGG C-3' (FRAG. NO:1549) (SEQ ID NO:10927)  
 5'-GGB GTT TCB TCT TGG-3' (FRAG. NO:1550) (SEQ ID NO:10928)  
 5'-GGB GTT TCB TCT TG-3' (FRAG. NO:1551) (SEQ ID NO:10929)  
 5'-GGB GTT TCB TCT T-3' (FRAG. NO:1552) (SEQ ID NO:10930)  
 5'-GGB GTT TCB TCT-3' (FRAG. NO:1553) (SEQ ID NO:10931)  
 55 5'-GB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1554) (SEQ ID NO:10932)  
 5'-GB GTT TCB TCT TGG CTT-3' (FRAG. NO:1555) (SEQ ID NO:10933)  
 5'-GB GTT TCB TCT TGG CT-3' (FRAG. NO:1556) (SEQ ID NO:10934)  
 5'-GB GTT TCB TCT TGG C-3' (FRAG. NO:1557) (SEQ ID NO:10935)  
 5'-GB GTT TCB TCT TGG-3' (FRAG. NO:1558) (SEQ ID NO:10936)  
 60 5'-GB GTT TCB TCT TG-3' (FRAG. NO:1559) (SEQ ID NO:10937)  
 5'-GB GTT TCB TCT T-3' (FRAG. NO:1560) (SEQ ID NO:10938)  
 5'-B GTT TCB TCT TGG CTT T-3' (FRAG. NO:1561) (SEQ ID NO:10939)  
 5'-B GTT TCB TCT TGG CTT-3' (FRAG. NO:1562) (SEQ ID NO:10940)  
 5'-B GTT TCB TCT TGG CTT-3' (FRAG. NO:1563) (SEQ ID NO:10941)  
 65 5'-B GTT TCB TCT TGG CT-3' (FRAG. NO:1564) (SEQ ID NO:10942)  
 5'-B GTT TCB TCT TGG C-3' (FRAG. NO:1565) (SEQ ID NO:10943)  
 5'-B GTT TCB TCT TGG-3' (FRAG. NO:1565) (SEQ ID NO:10944)  
 5'-B GTT TCB TCT TG-3' (FRAG. NO:1567) (SEQ ID NO:10945)  
 5'-GTT TCB TCT TGG CTT T-3' (FRAG. NO:1568) (SEQ ID NO:10946)  
 70 5'-GTT TCB TCT TGG CTT-3' (FRAG. NO:1569) (SEQ ID NO:10947)  
 5'-GTT TCB TCT TGG CT-3' (FRAG. NO:1570) (SEQ ID NO:10948)  
 5'-GTT TCB TCT TGG C-3' (FRAG. NO:1571) (SEQ ID NO:10949)  
 5'-GTT TCB TCT TGG-3' (FRAG. NO:1572) (SEQ ID NO:10950)  
 5'-TT TCB TCT TGG CTT T-3' (FRAG. NO:1573) (SEQ ID NO:10951)  
 75 5'-TT TCB TCT TGG CTT-3' (FRAG. NO:1574) (SEQ ID NO:10952)

- 5'-TT TCB TCT TGG CT-3' (FRAG. NO:1575)(SEQ ID NO:10953)  
 5'-TT TCB TCT TGG C-3' (FRAG. NO:1576)(SEQ ID NO:10954)  
 5'-T TCB TCT TGG CTT T-3' (FRAG. NO:1577)(SEQ ID NO:10955)  
 5'-T TCB TCT TGG CTT-3' (FRAG. NO:1578)(SEQ ID NO:10956)  
 5 5'-T TCB TCT TGG CT-3' (FRAG. NO:1579)(SEQ ID NO:10957)  
 5'-TCB TCT TGG CTT T-3' (FRAG. NO:1580)(SEQ ID NO:10958)  
 5'-TCB TCT TGG CTT-3' (FRAG. NO:1581)(SEQ ID NO:10959)  
 5'-GGG GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1582)(SEQ ID NO:10960)  
 5'-GG GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1583)(SEQ ID NO:10961)  
 10 5'-G GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1584)(SEQ ID NO:10962)  
 5'-GGB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1585)(SEQ ID NO:10963)  
 5'-GB GTT TCB TCT TGG CTT T-3' (FRAG. NO:1586)(SEQ ID NO:10964)  
 5'-B GTT TCB TCT TGG CTT T-3' (FRAG. NO:1587)(SEQ ID NO:10965)  
 5'-GTT TCB TCT TGG CTT T-3' (FRAG. NO:1588)(SEQ ID NO:10966)  
 15 5'-TT TCB TCT TGG CTT T-3' (FRAG. NO:1589)(SEQ ID NO:10967)  
 5'-T TCB TCT TGG CTT T-3' (FRAG. NO:1590)(SEQ ID NO:10968)  
 5'-TCB TCT TGG CTT T-3' (FRAG. NO:1591)(SEQ ID NO:10969)  
 5'-CB TCT TGG CTT T-3' (FRAG. NO:1592)(SEQ ID NO:10970)  
 5'-GGG GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1593)(SEQ ID NO:10971)  
 20 5'-GG GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1594)(SEQ ID NO:10972)  
 5'-G GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1595)(SEQ ID NO:10973)  
 5'-GGB GTT TCB TCT TGG CTT-3' (FRAG. NO:1596)(SEQ ID NO:10974)  
 5'-GB GTT TCB TCT TGG CTT-3' (FRAG. NO:1597)(SEQ ID NO:10975)  
 5'-B GTT TCB TCT TGG CTT-3' (FRAG. NO:1598)(SEQ ID NO:10976)  
 25 5'-GTT TCB TCT TGG CTT-3' (FRAG. NO:1599)(SEQ ID NO:10977)  
 5'-TT TCB TCT TGG CTT-3' (FRAG. NO:1600)(SEQ ID NO:10978)  
 5'-T TCB TCT TGG CTT-3' (FRAG. NO:1601)(SEQ ID NO:10979)  
 5'-TCB TCT TGG CTT-3' (FRAG. NO:1602)(SEQ ID NO:10980)  
 5'-GGG GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1603)(SEQ ID NO:10981)  
 30 5'-GG GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1604)(SEQ ID NO:10982)  
 5'-G GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1605)(SEQ ID NO:10983)  
 5'-GGB GTT TCB TCT TGG CT-3' (FRAG. NO:1606)(SEQ ID NO:10984)  
 5'-GB GTT TCB TCT TGG CT-3' (FRAG. NO:1607)(SEQ ID NO:10985)  
 5'-B GTT TCB TCT TGG CT-3' (FRAG. NO:1608)(SEQ ID NO:10986)  
 35 5'-GTT TCB TCT TGG CT-3' (FRAG. NO:1609)(SEQ ID NO:10987)  
 5'-TT TCB TCT TGG CT-3' (FRAG. NO:1610)(SEQ ID NO:10988)  
 5'-T TCB TCT TGG CT-3' (FRAG. NO:1611)(SEQ ID NO:10989)  
 5'-GGG GGB GTT TCB TCT TGG C-3' (FRAG. NO:1612)(SEQ ID NO:10990)  
 5'-GG GGB GTT TCB TCT TGG C-3' (FRAG. NO:1613)(SEQ ID NO:10991)  
 40 5'-G GGB GTT TCB TCT TGG C-3' (FRAG. NO:1614)(SEQ ID NO:10992)  
 5'-GGB GTT TCB TCT TGG C-3' (FRAG. NO:1615)(SEQ ID NO:10993)  
 5'-GB GTT TCB TCT TGG C-3' (FRAG. NO:1616)(SEQ ID NO:10994)  
 5'-B GTT TCB TCT TGG C-3' (FRAG. NO:1617)(SEQ ID NO:10995)  
 5'-GTT TCB TCT TGG C-3' (FRAG. NO:1618)(SEQ ID NO:10996)  
 45 5'-TT TCB TCT TGG C-3' (FRAG. NO:1619)(SEQ ID NO:10997)  
 5'-GGG GGB GTT TCB TCT TGG-3' (FRAG. NO:1620)(SEQ ID NO:10998)  
 5'-GG GGB GTT TCB TCT TGG-3' (FRAG. NO:1621)(SEQ ID NO:10999)  
 5'-G GGB GTT TCB TCT TGG-3' (FRAG. NO:1622)(SEQ ID NO:11000)  
 5'-GGB GTT TCB TCT TGG-3' (FRAG. NO:1623)(SEQ ID NO:11001)  
 50 5'-GB GTT TCB TCT TGG-3' (FRAG. NO:1624)(SEQ ID NO:11002)  
 5'-B GTT TCB TCT TGG-3' (FRAG. NO:1625)(SEQ ID NO:11003)  
 5'-GTT TCB TCT TGG-3' (FRAG. NO:1626)(SEQ ID NO:11004)  
 5'-GGG GGB GTT TCB TCT TG-3' (FRAG. NO:1627)(SEQ ID NO:11005)  
 5'-GG GGB GTT TCB TCT TG-3' (FRAG. NO:1628)(SEQ ID NO:11006)  
 55 5'-G GGB GTT TCB TCT TG-3' (FRAG. NO:1629)(SEQ ID NO:11007)  
 5'-GGB GTT TCB TCT TG-3' (FRAG. NO:1630)(SEQ ID NO:11008)  
 5'-GB GTT TCB TCT TG-3' (FRAG. NO:1631)(SEQ ID NO:11009)  
 5'-B GTT TCB TCT TG-3' (FRAG. NO:1632)(SEQ ID NO:11010)  
 5'-GGG GGB GTT TCB TCT T-3' (FRAG. NO:1633)(SEQ ID NO:11011)  
 60 5'-GG GGB GTT TCB TCT T-3' (FRAG. NO:1634)(SEQ ID NO:11012)  
 5'-G GGB GTT TCB TCT T-3' (FRAG. NO:1635)(SEQ ID NO:11013)  
 5'-G GGB GTT TCB TCT T-3' (FRAG. NO:1636)(SEQ ID NO:11014)  
 5'-GGB GTT TCB TCT T-3' (FRAG. NO:1637)(SEQ ID NO:11015)  
 5'-GB GTT TCB TCT T-3' (FRAG. NO:1638)(SEQ ID NO:11016)  
 65 5'-GGG GGB GTT TCB TCT-3' (FRAG. NO:1639)(SEQ ID NO:11017)  
 5'-GG GGB GTT TCB TCT-3' (FRAG. NO:1640)(SEQ ID NO:11018)  
 5'-G GGB GTT TCB TCT-3' (FRAG. NO:1641)(SEQ ID NO:11019)  
 5'-GGB GTT TCB TCT-3' (FRAG. NO:1642)(SEQ ID NO:11020)  
 5'-GGG GGB GTT TCB TC-3' (FRAG. NO:1643)(SEQ ID NO:11021)  
 70 5'-GG GGB GTT TCB TC-3' (FRAG. NO:1644)(SEQ ID NO:11022)  
 5'-G GGB GTT TCB TC-3' (FRAG. NO:1645)(SEQ ID NO:11023)  
 5'-GGG GGB GTT TCB T-3' (FRAG. NO:1646)(SEQ ID NO:11024)  
 5'-GG GGB GTT TCB T-3' (FRAG. NO:1647)(SEQ ID NO:11025)  
 5'-GGG GGB GTT TCB-3' (FRAG. NO:1648)(SEQ ID NO:11026)  
 75 5'-TCT CCC CTT GTT CCT CCC C-3' (FRAG. NO:1649)(SEQ ID NO:11027)

5'-TCT CCT GCT CTG GTG TCT CCT C-3' (FRAG. NO:1650)(SEQ ID NO:11028)  
 5'-TTC CCT CCC TCC CCT GCC-3' (FRAG. NO:1651)(SEQ ID NO:11029)  
 5'-GTG TTG TCT GTG GGT GTC C-3' (FRAG. NO:1652)(SEQ ID NO:11030)  
 5'-GTT TCG CTC TTG TTG CCC-3' (FRAG. NO:1653)(SEQ ID NO:10891)  
 5'-TGG GCC CTT CCC TGC TGG-3' (FRAG. NO:1654)(SEQ ID NO:11032)  
 5'-GGG GGB G-3' (FRAG. NO:1912)(SEQ ID NO:11294)  
 5'-GTG GGT GTC C-3' (FRAG. NO:1913) (SEQ ID NO:11295)

#### **BP-1 Nucleic Acids and Antisense Oligonucleotide Fragments**

5'-CCGTGTTGTC BGTGGTGTG CCCGTTTGBG GTBTGGCGCT CCBCBBTTC CCTTTTCTCC TTGTTTTCCG TTCTCTTGC  
 10 CGTCTGTGGT T-3' (FRAG. NO:1914) (SEQ ID NO:11296)  
 5'-CCCGTTTGBGGTBTGGC-3'(FRAG. NO:1915) (SEQ ID NO:11297)  
 5'-GCTCCBCCBBTTCCTTTTCTCC-3'(FRAG. NO:1916) (SEQ ID NO:11298)  
 5'-TTGTTTTCCGTTTCTCTTG-3'(FRAG. NO:1917) (SEQ ID NO:11299)  
 5'-CCGTCTGTGGT-3'(FRAG. NO:1918) (SEQ ID NO:11300)  
 15 5'-CCCGTTTGAGGTATGGC-3'(FRAG. NO:1919) (SEQ ID NO:11301)  
 5'-GCTCCBCCAATTCCCTTTTCTCC-3'(FRAG. NO:1920) (SEQ ID NO:11302)

#### **C/EBPNucleic Acids and Antisense Oligonucleotide Antisense Oligonucleotide Fragments**

5'-GGGCCCBGCCCCGCCGCTTTTCTBGCCCC GGCC-3' (FRAG. NO:1921) (SEQ ID NO:11303)  
 5'-GGGCCCBGCCCCGCCGCTTTTCTBGCCCC GGC-3' (FRAG. NO:1922) (SEQ ID NO:11304)  
 20 5'-GGGCCCB GCCCGCCGCTTTTCTBGCCCCG-3' (FRAG. NO:1923) (SEQ ID NO:11305)  
 5'-GGGCCCBGCCCCGCCGCTTTTCTBGCCCCG-3' (FRAG. NO:1924) (SEQ ID NO:11306)  
 5'-GGGCCCBGCCCCGCCGCTTTTCTBGCCCC-3' (FRAG. NO:1925) (SEQ ID NO:11307)  
 5'-GGGCCCBGCCCCGCCGCTTTTCTBGCCCC-3' (FRAG. NO:1926) (SEQ ID NO:11308)  
 5'-GGGCCCBGCCCCGCCGCTTTTCTBGCC-3' (FRAG. NO:1927) (SEQ ID NO:11309)  
 25 5'-GGGCCCBGCCCCGCCGCTTTTCTBGCC-3' (FRAG. NO:1928) (SEQ ID NO:11310)  
 5'-GGGCCCBGCCCCGCCGCTTTTCTBG-3' (FRAG. NO:1929) (SEQ ID NO:11311)  
 5'-GGGCCCBGCCCCGCCGCTTTTCTB-3' (FRAG. NO:1930) (SEQ ID NO:11312)  
 5'-GGGCCCBGCCCCGCCGCTTTTCT-3' (FRAG. NO:1931) (SEQ ID NO:11311) 1944)  
 5'-GGGCCCBGCCCCGCCGCTTTTC-3' (FRAG. NO:1932) (SEQ ID NO:11314)  
 30 5'-GGGCCCBGCCCCGCCGCTTTT-3' (FRAG. NO:1933) (SEQ ID NO:11315)  
 5'-GGGCCCBGCCCCGCCGCTTT-3' (FRAG. NO:1934) (SEQ ID NO:11316) [1945])  
 5'-GGGCCCBGCCCCGCCGCTT-3' (FRAG. NO:1935) (SEQ ID NO:11317)  
 5'-GGGCCCBGCCCCGCCGCT-3' (FRAG. NO:1936) (SEQ ID NO:11318)  
 5'-GGGCCCBGCCCCGCCG-3' (FRAG. NO:1937) (SEQ ID NO:11319)  
 35 5'-GGGCCCBGCCCCGCC-3' (FRAG. NO:1938) (SEQ ID NO:11320)  
 5'-GGGCCCBGCCCCGC-3' (FRAG. NO:1939) (SEQ ID NO:11321)  
 5'-GGGCCCBGCCCCG-3' (FRAG. NO:1940) (SEQ ID NO:11322)  
 5'-GGGCCCBGCCCC-3' (FRAG. NO:1941) (SEQ ID NO:11323)  
 5'-GGGCCCBGCCCC-3' (FRAG. NO:1942) (SEQ ID NO:11324)  
 40 5'-GGGCCCBGCCCC-3' (FRAG. NO:1943) (SEQ ID NO:11325)  
 5'-GGGCCCBGCCCC-3' (FRAG. NO:1944) (SEQ ID NO:11326)  
 5'-GGGCCBCCCCGCCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1945) (SEQ ID NO:11327)  
 5'-GCCCCBCCCCGCCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1946) (SEQ ID NO:11328)  
 5'-CCCBGCCCCGCCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1947) (SEQ ID NO:11329)  
 45 5'-CCBGCCCCGCCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1948) (SEQ ID NO:11330)  
 5'-CBGCCCCGCCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1948) (SEQ ID NO:11331)  
 5'-BGCCCCGCCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1950) (SEQ ID NO:11332)  
 5'-GCCCGCCGCTTTTCTBGCCCCGGC-3' (FRAG. NO:1951) (SEQ ID NO:11333)  
 5'-CCCCGCCGCTTTTCTBGCCCCGGC-3' (FRAG. NO:1952) (SEQ ID NO:11334)  
 50 5'-CCCGCCGCTTTTCTBGCCCCGGC-3' (FRAG. NO:1953) (SEQ ID NO:11335)  
 5'-CCGCCGCTTTTCTBGCCCCGGC-3' (FRAG. NO:1954) (SEQ ID NO:11336)  
 5'-CGCCGCTTTTCTBGCCCCGGC-3' (FRAG. NO:1955) (SEQ ID NO:11337)  
 5'-GCCGCTTTTCTBGCCCCGGC-3' (FRAG. NO:1956) (SEQ ID NO:11338)  
 5'-CCGCTTTTCTBGCCCCGGC-3' (FRAG. NO:1957) (SEQ ID NO:11339)  
 55 5'-CGCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1958) (SEQ ID NO:11340)  
 5'-GCCTTTTCTBGCCCCGGC-3' (FRAG. NO:1959) (SEQ ID NO:11341)  
 5'-CCTTTTCTBGCCCCGGC-3' (FRAG. NO:1960) (SEQ ID NO:11342)  
 5'-CTTTTCTBGCCCCGGC-3' (FRAG. NO:1961) (SEQ ID NO:11343)  
 5'-TTTTTCTBGCCCCGGC-3' (FRAG. NO:1962) (SEQ ID NO:11344)  
 60 5'-TTTCTBGCCCCGGC-3' (FRAG. NO:1963) (SEQ ID NO:11345)  
 5'-TTCTBGCCCCGGC-3' (FRAG. NO:1964) (SEQ ID NO:11346)  
 5'-TCTBGCCCCGGC-3' (FRAG. NO:1965) (SEQ ID NO:11347)  
 5'-CTBGCCCCGGC-3' (FRAG. NO:1966) (SEQ ID NO:11348)  
 5'-GCGBGCTGTBCCTCGCTGGGCC-3' (FRAG. NO:1967) (SEQ ID NO:11349)  
 65 5'-GCGBGCTGTBCCTCGCTGGGC-3' (FRAG. NO:1968) (SEQ ID NO:11350)  
 5'-GCGBGCTGTBCCTCGCTGGC-3' (FRAG. NO:1969) (SEQ ID NO:11351)  
 5'-GCGBGCTGTBCCTCGCTGG-3' (FRAG. NO:1970) (SEQ ID NO:11352)  
 5'-GCGBGCTGTBCCTCGTG-3' (FRAG. NO:1971) (SEQ ID NO:11353)  
 5'-GCGBGCTGTBCCTCG-3' (FRAG. NO:1972) (SEQ ID NO:11354)  
 70 5'-GCGBGCTGTBCCTC-3' (FRAG. NO:1973) (SEQ ID NO:11355)  
 5'-GCGBGCTGTBCCT-3' (FRAG. NO:1974) (SEQ ID NO:11356)  
 5'-GCGBGCTGTBC-3' (FRAG. NO:1975) (SEQ ID NO:11357)  
 5'-GCGBGCTGTBC-3' (FRAG. NO:1976) (SEQ ID NO:11358)  
 5'-GCGBGCTGT-3' (FRAG. NO:1977) (SEQ ID NO:11359)

- 5'-GCGBGGCTGTCCBCC-3' (FRAG. NO:1978) (SEQ ID NO:11360)  
 5'-GCGBGGCTGTCCBC-3' (FRAG. NO:1979) (SEQ ID NO:11361)  
 5'-GCGBGGCTGTCCB-3' (FRAG. NO:1980) (SEQ ID NO:11362)  
 5'-GCGBGGCTGTCC-3' (FRAG. NO:1981) (SEQ ID NO:11363)  
 5'-GCGBGGCTGT-3' (FRAG. NO:1982) (SEQ ID NO:11364)  
 5'-GCBGGCTGTCCCTCGCTGGGCCC-3' (FRAG. NO:1983) (SEQ ID NO:11365)  
 5'-GBGGCTGTCCCTCGCTGGGCCC-3' (FRAG. NO:1984) (SEQ ID NO:11366)  
 5'-BGGCTGTCCCTCGCTGGGCCC-3' (FRAG. NO:1985) (SEQ ID NO:11367)  
 5'-GGCTGTCCCTCGCTGGGCCC-3' (FRAG. NO:1986) (SEQ ID NO:11368)  
 5'-GCTGTCCCTCGCTGGGCCC-3' (FRAG. NO:1987) (SEQ ID NO:11369)  
 5'-CTGTCCCTCGCTGGGCCC-3' (FRAG. NO:1988) (SEQ ID NO:11370)  
 5'-TGTCBCTCGCTGGGCCC-3' (FRAG. NO:1989) (SEQ ID NO:11371)  
 5'-GTCBCTCGCTGGGCCC-3' (FRAG. NO:1990) (SEQ ID NO:11372)  
 5'-TCBCTCGCTGGGCCC-3' (FRAG. NO:1991) (SEQ ID NO:11373)  
 5'-CBCCTCGCTGGGCCC-3' (FRAG. NO:1992) (SEQ ID NO:11374)  
 5'-BCCTCGCTGGGCCC-3' (FRAG. NO:1993) (SEQ ID NO:11375)  
 5'-CCTCGCTGGGCCC-3' (FRAG. NO:1994) (SEQ ID NO:11376)  
 5'-CTCGCTGGGCCC-3' (FRAG. NO:1995) (SEQ ID NO:11377)  
 5'-TCGCTGGGCCC-3' (FRAG. NO:1996) (SEQ ID NO:11378)  
 5'-CGCTGGGCCC-3' (FRAG. NO:1997) (SEQ ID NO:11379)  
 5'-GCGCGGCGCTCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:1998) (SEQ ID NO:11380)  
 5'-GCGCGGCGCTCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:1999) (SEQ ID NO:11381)  
 5'-GCGCGGCGCTCBTGGCGGCGTCGGGCCGG-3' (FRAG. NO:2000) (SEQ ID NO:11382)  
 5'-GCGCGGCGCTCBTGGCGGCGTCGGGCCG-3' (FRAG. NO:2001) (SEQ ID NO:11383)  
 5'-GCGCGGCGCTCBTGGCGGCGTCGGGCC-3' (FRAG. NO:2002) (SEQ ID NO:11384)  
 5'-GCGCGGCGCTCBTGGCGGCGTCGGGC-3' (FRAG. NO:2003) (SEQ ID NO:11385)  
 5'-GCGCGGCGCTCBTGGCGGCGTCGGG-3' (FRAG. NO:2004) (SEQ ID NO:11386)  
 5'-GCGCGGCGCTCBTGGCGGCGTCGG-3' (FRAG. NO:2005) (SEQ ID NO:11387)  
 5'-GCGCGGCGCTCBTGGCGGCGTCGG-3' (FRAG. NO:2006) (SEQ ID NO:11388)  
 5'-GCGCGGCGCTCBTGGCGGCGTC-3' (FRAG. NO:2007) (SEQ ID NO:11389)  
 5'-GCGCGGCGCTCBTGGCGGCGT-3' (FRAG. NO:2008) (SEQ ID NO:11390)  
 5'-GCGCGGCGCTCBTGGCGGCG-3' (FRAG. NO:2009) (SEQ ID NO:11391)  
 5'-GCGCGGCGCTCBTGGCGG-3' (FRAG. NO:2010) (SEQ ID NO:11392)  
 5'-GCGCGGCGCTCBTGGCG-3' (FRAG. NO:2011) (SEQ ID NO:11393)  
 5'-GCGCGGCGCTCBTGGC-3' (FRAG. NO:2012) (SEQ ID NO:11394)  
 5'-GCGCGGCGCTCBTGG-3' (FRAG. NO:2013) (SEQ ID NO:11395)  
 5'-GCGCGGCGCTCBTG-3' (FRAG. NO:2014) (SEQ ID NO:11396)  
 5'-GCGCGGCGCTCB-3' (FRAG. NO:2015) (SEQ ID NO:11397)  
 5'-GCGCGGCGCTB-3' (FRAG. NO:2016) (SEQ ID NO:11398)  
 5'-GCGCGGCGCTC-3' (FRAG. NO:2017) (SEQ ID NO:11399)  
 5'-GCGCGGCGTC-3' (FRAG. NO:2018) (SEQ ID NO:11400)  
 5'-GCGCGGCGT-3' (FRAG. NO:2019) (SEQ ID NO:11401)  
 5'-GCGGCGCGCTCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2020) (SEQ ID NO:11402)  
 5'-GCGGCGCGCTCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2021) (SEQ ID NO:11403)  
 5'-CGGCGCTCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2022) (SEQ ID NO:11404)  
 5'-GGCGCTCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2023) (SEQ ID NO:11405)  
 5'-GCGCTCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2024) (SEQ ID NO:11406)  
 5'-CCGCTCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2025) (SEQ ID NO:11407)  
 5'-CGTCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2026) (SEQ ID NO:11408)  
 5'-GTCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2027) (SEQ ID NO:11409)  
 5'-TCBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2028) (SEQ ID NO:11410)  
 5'-CBTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2029) (SEQ ID NO:11411)  
 5'-BTGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2030) (SEQ ID NO:11412)  
 5'-TGGCGGCGTCGGGCCGGG-3' (FRAG. NO:2031) (SEQ ID NO:11413)  
 5'-GGCGGCGTCGGGCCGGG-3' (FRAG. NO:2032) (SEQ ID NO:11414)  
 5'-GCGGCGTCGGGCCGGG-3' (FRAG. NO:2033) (SEQ ID NO:11415)  
 5'-CGGCGTCGGGCCGGG-3' (FRAG. NO:2034) (SEQ ID NO:11416)  
 5'-GGCGTCGGGCCGGG-3' (FRAG. NO:2035) (SEQ ID NO:11417)  
 5'-GCGTCGGGCCGGG-3' (FRAG. NO:2036) (SEQ ID NO:11418)  
 5'-CGTCGGGCCGGG-3' (FRAG. NO:2037) (SEQ ID NO:11419)  
 5'-GTCGGGCCGGG-3' (FRAG. NO:2038) (SEQ ID NO:11420)  
 5'-TCGGGCCGGG-3' (FRAG. NO:2039) (SEQ ID NO:11421)  
 5'-CGGGCCGGG-3' (FRAG. NO:2040) (SEQ ID NO:11422)  
 5'-CCGCBGGCCBGGGCGCGCCGCGGCCGGG-3' (FRAG. NO:2041) (SEQ ID NO:11423)  
 5'-CCGCBGGCCBGGGCGCGCCGCGGCCGGG-3' (FRAG. NO:2042) (SEQ ID NO:11424)  
 5'-CCGCBGGCCBGGGCGCGCCGCGGCCGGG-3' (FRAG. NO:2043) (SEQ ID NO:11425)  
 5'-CCGCBGGCCBGGGCGCGCCGCGGCCGGG-3' (FRAG. NO:2044) (SEQ ID NO:11426)  
 5'-CCGCBGGCCBGGGCGCGCCGCGGCCGGG-3' (FRAG. NO:2045) (SEQ ID NO:11427)  
 5'-CCGCBGGCCBGGGCGCGCCGCGGCCGGG-3' (FRAG. NO:2046) (SEQ ID NO:11428)  
 5'-CCGCBGGCCBGGGCGCGCCGCGGCC-3' (FRAG. NO:2047) (SEQ ID NO:11429)  
 5'-CCGCBGGCCBGGGCGCGCCGCGGC-3' (FRAG. NO:2048) (SEQ ID NO:11430)  
 5'-CCGCBGGCCBGGGCGCGCCCGG-3' (FRAG. NO:2049) (SEQ ID NO:11431)  
 5'-CCGCBGGCCBGGGCGCGCCCG-3' (FRAG. NO:2050) (SEQ ID NO:11432)  
 5'-CCGCBGGCCBGGGCGCGCCG-3' (FRAG. NO:2051) (SEQ ID NO:11433)  
 5'-CCGCBGGCCBGGGCGCGC-3' (FRAG. NO:2052) (SEQ ID NO:11434)

- 5'-CCGCBGGCCBGGGCGCGCCG-3' (FRAG. NO:2053) (SEQ ID NO:11435)  
5'-CCGCBGGCCBGGGCGCGCC-3' (FRAG. NO:2054) (SEQ ID NO:11436)  
5'-CCGCBGGCCBGGGCGCGC-3' (FRAG. NO:2055) (SEQ ID NO:11437)  
5'-CCGCBGGCCBGGGCGCG-3' (FRAG. NO:2056) (SEQ ID NO:11438)  
5 5'-CCGCBGGCCBGGGCGC-3' (FRAG. NO:2057) (SEQ ID NO:11439)  
5'-CCGCBGGCCBGGGCG-3' (FRAG. NO:2058) (SEQ ID NO:11440)  
5'-CCGCBGGCCBGGGC-3' (FRAG. NO:2059) (SEQ ID NO:11441)  
5'-CCGCBGGCCBGGG-3' (FRAG. NO:2060) (SEQ ID NO:11442)  
5'-CCGCBGGCCBGG-3' (FRAG. NO:2061) (SEQ ID NO:11443)  
10 5'-CCGCBGGCCB-3' (FRAG. NO:2062) (SEQ ID NO:11444)  
5'-CCGCBGGCC-3' (FRAG. NO:2063) (SEQ ID NO:11445)  
5'-CCGCBGGC-3' (FRAG. NO:2064) (SEQ ID NO:11446)  
5'-CGCBGGCCBGGGCGCGCCGCGCGCCGCG-3' (FRAG. NO:2065) (SEQ ID NO:11447)  
5'-GCBGGCCBGGGCGCGCCGCGCGCCGCGCGCG-3' (FRAG. NO:2066) (SEQ ID NO:11448)  
15 5'-CBGGCCBGGGCGCGCCGCGCGCGCGCGCGCG-3' (FRAG. NO:2067) (SEQ ID NO:11449)  
5'-BGGCCBGGGCGCGCCGCGCGCGCGCGCGCG-3' (FRAG. NO:2068) (SEQ ID NO:11450)  
5'-GGCCBGGGCGCGCCGCGCGCGCGCGCGCG-3' (FRAG. NO:2069) (SEQ ID NO:11451)  
5'-GCCBGGGCGCGCCGCGCGCGCGCGCGCG-3' (FRAG. NO:2070) (SEQ ID NO:11452)  
5'-CCBGGGCGCGCCGCGCGCGCGCGCGCG-3' (FRAG. NO:2071) (SEQ ID NO:11453)  
20 5'-CBGGGCGCGCCGCGCGCGCGCGCGCG-3' (FRAG. NO:2072) (SEQ ID NO:11454)  
5'-BGGGCGCGCCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2073) (SEQ ID NO:11455)  
5'-GGGCGCGCCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2074) (SEQ ID NO:11456)  
5'-GGCGCGCCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2075) (SEQ ID NO:11457)  
5'-GCGCGCCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2076) (SEQ ID NO:11458)  
25 5'-CGCGCCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2077) (SEQ ID NO:11459)  
5'-GCGCCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2078) (SEQ ID NO:11460)  
5'-CGCCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2079) (SEQ ID NO:11461)  
5'-GCCCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2080) (SEQ ID NO:11462)  
5'-CCGCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2081) (SEQ ID NO:11463)  
30 5'-CGCCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2082) (SEQ ID NO:11464)  
5'-GCCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2083) (SEQ ID NO:11465)  
5'-CCGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2084) (SEQ ID NO:11466)  
5'-CGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2085) (SEQ ID NO:11467)  
5'-GGCGCGCGCGCGCGCGCG-3' (FRAG. NO:2086) (SEQ ID NO:11468)  
35 5'-GGGCGCBGGCTCCGCB-3' (FRAG. NO:2087) (SEQ ID NO:11469)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCGCGCG-3' (FRAG. NO:2088) (SEQ ID NO:11470)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCGCGCG-3' (FRAG. NO:2089) (SEQ ID NO:11471)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCGCGCG-3' (FRAG. NO:2090) (SEQ ID NO:11472)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCGCGCG-3' (FRAG. NO:2091) (SEQ ID NO:11473)  
40 5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCGCG-3' (FRAG. NO:2092) (SEQ ID NO:11474)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCG-3' (FRAG. NO:2093) (SEQ ID NO:11475)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCG-3' (FRAG. NO:2094) (SEQ ID NO:11476)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCC-3' (FRAG. NO:2095) (SEQ ID NO:11477)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGC-3' (FRAG. NO:2096) (SEQ ID NO:11478)  
45 5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCGC-3' (FRAG. NO:2097) (SEQ ID NO:11479)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCG-3' (FRAG. NO:2098) (SEQ ID NO:11480)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCC-3' (FRAG. NO:2099) (SEQ ID NO:11481)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTG-3' (FRAG. NO:2100) (SEQ ID NO:11482)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTG-3' (FRAG. NO:2101) (SEQ ID NO:11483)  
50 5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCT-3' (FRAG. NO:2102) (SEQ ID NO:11484)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTT-3' (FRAG. NO:2103) (SEQ ID NO:11485)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCT-3' (FRAG. NO:2104) (SEQ ID NO:11486)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGG-3' (FRAG. NO:2105) (SEQ ID NO:11487)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCG-3' (FRAG. NO:2106) (SEQ ID NO:11488)  
55 5'-GGGCCCTGGCTCGGCCCGCGCGCCCG-3' (FRAG. NO:2107) (SEQ ID NO:11489)  
5'-GGGCCCTGGCTCGGCCCGCGCGCC-3' (FRAG. NO:2108) (SEQ ID NO:11490)  
5'-GGGCCCTGGCTCGGCCCGCGCG-3' (FRAG. NO:2109) (SEQ ID NO:11491)  
5'-GGGCCCTGGCTCGGCCCGCG-3' (FRAG. NO:2110) (SEQ ID NO:11492)  
5'-GGGCCCTGGCTCGGCCCG-3' (FRAG. NO:2111) (SEQ ID NO:11493)  
60 5'-GGGCCCTGGCTCGGCCG-3' (FRAG. NO:2112) (SEQ ID NO:11494)  
5'-GGGCCCTGGCTCGGCC-3' (FRAG. NO:2113) (SEQ ID NO:11495)  
5'-GGGCCCTGGCTCGGC-3' (FRAG. NO:2114) (SEQ ID NO:11496)  
5'-GGGCCCTGGCTCGG-3' (FRAG. NO:2115) (SEQ ID NO:11497)  
5'-GGGCCCTGGCTCG-3' (FRAG. NO:2116) (SEQ ID NO:11498)  
65 5'-GGGCCCTGGCTCG-3' (FRAG. NO:2117) (SEQ ID NO:11499)  
5'-GGGCCCTGGCTCG-3' (FRAG. NO:2118) (SEQ ID NO:11500)  
5'-GGGCCCTGGCTCG-3' (FRAG. NO:2119) (SEQ ID NO:11501)  
5'-GGGCCCTGGCTCG-3' (FRAG. NO:2120) (SEQ ID NO:11502)  
5'-GGGCCCTGGCTC-3' (FRAG. NO:2121) (SEQ ID NO:11503)  
70 5'-GGGCCCTGGCT-3' (FRAG. NO:2122) (SEQ ID NO:11504)  
5'-GGGCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCGCGCG-3' (FRAG. NO:2123) (SEQ ID NO:11505)  
5'-GCCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCGCGCG-3' (FRAG. NO:2124) (SEQ ID NO:11506)  
5'-CCCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCGCGCG-3' (FRAG. NO:2125) (SEQ ID NO:11507)  
5'-CCTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCGCGCG-3' (FRAG. NO:2126) (SEQ ID NO:11508)  
75 5'-CTGGCTCGGCCCGCGCGCCCGGCTTGCCCGCCCGCGCGCG-3' (FRAG. NO:2127) (SEQ ID NO:11509)



5'-CTGGCTCGGCCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2128) (SEQ ID NO:11510)  
5'-TGGCTCGGCCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2129) (SEQ ID NO:11511)  
5'-GGCTCGGCCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2130) (SEQ ID NO:11512)  
5'-GCTCGGCCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2131) (SEQ ID NO:11513)  
5'-CTCGGCCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2132) (SEQ ID NO:11514)  
5'-TCGGCCCCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2133) (SEQ ID NO:11515)  
5'-CGGCCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2134) (SEQ ID NO:11516)  
5'-GGCCCCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2135) (SEQ ID NO:11517)  
5'-GCCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2136) (SEQ ID NO:11518)  
5'-CCCCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2137) (SEQ ID NO:11519)  
5'-CCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2138) (SEQ ID NO:11520)  
5'-CCCGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2139) (SEQ ID NO:11521)  
5'-CGCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2140) (SEQ ID NO:11522)  
5'-GCGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2141) (SEQ ID NO:11523)  
5'-CGGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2142) (SEQ ID NO:11524)  
5'-GGCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2143) (SEQ ID NO:11525)  
5'-GCCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2144) (SEQ ID NO:11526)  
5'-CCCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2145) (SEQ ID NO:11527)  
5'-CCGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2146) (SEQ ID NO:11528)  
5'-CGGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2147) (SEQ ID NO:11529)  
5'-GGCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2148) (SEQ ID NO:11530)  
5'-GCTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2149) (SEQ ID NO:11531)  
5'-CTTGCCCGCCCGGCCCGG-3' (FRAG. NO:2150) (SEQ ID NO:11532)  
5'-TTGCCCGCCCGGCCCGG-3' (FRAG. NO:2151) (SEQ ID NO:11533)  
5'-TGCCCGCCCGGCCCGG-3' (FRAG. NO:2152) (SEQ ID NO:11534)  
5'-GCCCGCCCGGCCCGG-3' (FRAG. NO:2153) (SEQ ID NO:11535)  
5'-CCCGCCCGGCCCGG-3' (FRAG. NO:2154) (SEQ ID NO:11536)  
5'-CCGCCCGGCCCGG-3' (FRAG. NO:2155) (SEQ ID NO:11537)  
5'-CGCCCGGCCCGG-3' (FRAG. NO:2156) (SEQ ID NO:11538)  
5'-GCCCGGCCCGG-3' (FRAG. NO:2157) (SEQ ID NO:11539)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2158) (SEQ ID NO:11540)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2159) (SEQ ID NO:11541)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGCCTBGGGCC-3' (FRAG. NO:2160) (SEQ ID NO:11542)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGCCTBGGGC-3' (FRAG. NO:2161) (SEQ ID NO:11543)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGCCTBGGG-3' (FRAG. NO:2162) (SEQ ID NO:11544)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGCCTBGG-3' (FRAG. NO:2163) (SEQ ID NO:11545)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGCCTBG-3' (FRAG. NO:2164) (SEQ ID NO:11546)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGCCTB-3' (FRAG. NO:2165) (SEQ ID NO:11547)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGCCT-3' (FRAG. NO:2166) (SEQ ID NO:11548)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGCC-3' (FRAG. NO:2167) (SEQ ID NO:11549)  
5'-GGCGGGGGCGGCGCGCCTGGCTCGC-3' (FRAG. NO:2168) (SEQ ID NO:11550)  
5'-GGCGGGGGCGGCGCGCCTGGCTCG-3' (FRAG. NO:2169) (SEQ ID NO:11551)  
5'-GGCGGGGGCGGCGCGCCTGGCTC-3' (FRAG. NO:2170) (SEQ ID NO:11552)  
5'-GGCGGGGGCGGCGCGCCTGGCT-3' (FRAG. NO:2171) (SEQ ID NO:11553)  
5'-GGCGGGGGCGGCGCGCCTGGC-3' (FRAG. NO:2172) (SEQ ID NO:11554)  
5'-GGCGGGGGCGGCGCGCCTGG-3' (FRAG. NO:2173) (SEQ ID NO:11555)  
5'-GGCGGGGGCGGCGCGCCTG-3' (FRAG. NO:2174) (SEQ ID NO:11556)  
5'-GGCGGGGGCGGCGCGCCT-3' (FRAG. NO:2175) (SEQ ID NO:11557)  
5'-GGCGGGGGCGGCGCGCC-3' (FRAG. NO:2176) (SEQ ID NO:11558)  
5'-GGCGGGGGCGGCGGCGC-3' (FRAG. NO:2177) (SEQ ID NO:11559)  
5'-GGCGGGGGCGGCGGCG-3' (FRAG. NO:2178) (SEQ ID NO:11560)  
5'-GGCGGGGGCGGCGGC-3' (FRAG. NO:2179) (SEQ ID NO:11561)  
5'-GGCGGGGGCGGCGG-3' (FRAG. NO:2180) (SEQ ID NO:11562)  
5'-GGCGGGGGCGGCG-3' (FRAG. NO:2181) (SEQ ID NO:11563)  
5'-GGCGGGGGCGGC-3' (FRAG. NO:2182) (SEQ ID NO:11564)  
5'-GGCGGGGGCGG-3' (FRAG. NO:2183) (SEQ ID NO:11565)  
5'-GCGGGGGCGGCGGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2184) (SEQ ID NO:11566)  
5'-CGGGGGCGGCGGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2185) (SEQ ID NO:11567)  
5'-GGGGCGGCGGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2186) (SEQ ID NO:11568)  
5'-GGGGCGGCGGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2187) (SEQ ID NO:11569)  
5'-GGGGCGGCGGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2188) (SEQ ID NO:11570)  
5'-GGGGCGGCGGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2189) (SEQ ID NO:11571)  
5'-GCGGCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2190) (SEQ ID NO:11572)  
5'-CGGCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2191) (SEQ ID NO:11573)  
5'-GCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2192) (SEQ ID NO:11574)  
5'-GCGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2193) (SEQ ID NO:11575)  
5'-CGGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2194) (SEQ ID NO:11576)  
5'-GGCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2195) (SEQ ID NO:11577)  
5'-GCGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2196) (SEQ ID NO:11578)  
5'-CGCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2197) (SEQ ID NO:11579)  
5'-GCCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2198) (SEQ ID NO:11580)  
5'-CCTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2199) (SEQ ID NO:11581)  
5'-CTGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2200) (SEQ ID NO:11582)  
5'-TGGCTCGCCTBGGGCCCC-3' (FRAG. NO:2201) (SEQ ID NO:11583)  
5'-GGCTCGCCTBGGGCCCC-3' (FRAG. NO:2202) (SEQ ID NO:11584)

- 5'-GCTCGCCTBGGGCCCC-3' (FRAG. NO:2203) (SEQ ID NO:11585)  
 5'-CTCGCCTBGGGCCCC-3' (FRAG. NO:2204) (SEQ ID NO:11586)  
 5'-TCGCCTBGGGCCCC-3' (FRAG. NO:2205) (SEQ ID NO:11587)  
 5'-CGCCTBGGGCCCC-3' (FRAG. NO:2206) (SEQ ID NO:11588)  
 5'-GCCTBGGGCCCC-3' (FRAG. NO:2207) (SEQ ID NO:11589)  
 5'-CTBGGGCCCC-3' (FRAG. NO:2208) (SEQ ID NO:11590)  
 5'-CTBGGGCCCC-3' (FRAG. NO:2209) (SEQ ID NO:11591)  
 5'-GGGTGGGCBGCGCGGCC-3' (FRAG. NO:2210) (SEQ ID NO:11592)  
 5'-GGTCGGCGBBBGBGCTCGTCGTGGC-3' (FRAG. NO:2211) (SEQ ID NO:11593)  
 5'-GGTCGGCGBBBGBGCTCGTCGTGG-3' (FRAG. NO:2212) (SEQ ID NO:11594)  
 5'-GGTCGGCGBBBGBGCTCGTCGTG-3' (FRAG. NO:2213) (SEQ ID NO:11595)  
 5'-GGTCGGCGBBBGBGCTCGTCGT-3' (FRAG. NO:2214) (SEQ ID NO:11596)  
 5'-GGTCGGCGBBBGBGCTCGTCG-3' (FRAG. NO:2215) (SEQ ID NO:11597)  
 5'-GGTCGGCGBBBGBGCTCGTC-3' (FRAG. NO:2216) (SEQ ID NO:11598)  
 5'-GGTCGGCGBBBGBGCTCGT-3' (FRAG. NO:2217) (SEQ ID NO:11599)  
 5'-GGTCGGCGBBBGBGCTCG-3' (FRAG. NO:2218) (SEQ ID NO:11600)  
 5'-GGTCGGCGBBBGBGCTC-3' (FRAG. NO:2219) (SEQ ID NO:11601)  
 5'-GGTCGGCGBBBGBGCT-3' (FRAG. NO:2220) (SEQ ID NO:11602)  
 5'-GGTCGGCGBBBGBGC-3' (FRAG. NO:2221) (SEQ ID NO:11603)  
 5'-GGTCGGCGBBBGBG-3' (FRAG. NO:2222) (SEQ ID NO:11604)  
 5'-GGTCGGCGBBBGB-3' (FRAG. NO:2223) (SEQ ID NO:11605)  
 5'-GGTCGGCGBBG-3' (FRAG. NO:2224) (SEQ ID NO:11606)  
 5'-GTCGGCGBBBGBGCTCGTCGTGGC-3' (FRAG. NO:2225) (SEQ ID NO:11607)  
 5'-TCGGCGBBBGBGCTCGTCGTGGC-3' (FRAG. NO:2226) (SEQ ID NO:11608)  
 5'-CGGCGBBBGBGCTCGTCGTGGC-3' (FRAG. NO:2227) (SEQ ID NO:11609)  
 5'-GGCGBBBGBGCTCGTCGTGGC-3' (FRAG. NO:2228) (SEQ ID NO:11610)  
 5'-GCGBBBGBGCTCGTCGTGGC-3' (FRAG. NO:2229) (SEQ ID NO:11611)  
 5'-CGBBBGBGCTCGTCGTGGC-3' (FRAG. NO:2230) (SEQ ID NO:11612)  
 5'-GBBBGBGCTCGTCGTGGC-3' (FRAG. NO:2231) (SEQ ID NO:11613)  
 5'-BBBGBGCTCGTCGTGGC-3' (FRAG. NO:2232) (SEQ ID NO:11614)  
 5'-BGBGCTCGTCGTGGC-3' (FRAG. NO:2233) (SEQ ID NO:11615)  
 5'-GBGCTCGTCGTGGC-3' (FRAG. NO:2234) (SEQ ID NO:11616)  
 5'-BGCTCGTCGTGGC-3' (FRAG. NO:2235) (SEQ ID NO:11617)  
 5'-GCTCGTCGTGGC-3' (FRAG. NO:2236) (SEQ ID NO:11618)  
 5'-CTCGTCGTGGC-3' (FRAG. NO:2237) (SEQ ID NO:11619)  
 5'-TCGTCGTGGC-3' (FRAG. NO:2238) (SEQ ID NO:11620)  
 5'-GGGGCCCCGCGCGCCCGCC-3' (FRAG. NO:2239) (SEQ ID NO:11621)  
 5'-GGGGCCCCGCGCGCCCGC-3' (FRAG. NO:2240) (SEQ ID NO:11622)  
 5'-GGGGCCCCGCGCGCCCG-3' (FRAG. NO:2241) (SEQ ID NO:11623)  
 5'-GGGGCCCCGCGCGCC-3' (FRAG. NO:2242) (SEQ ID NO:11624)  
 5'-GGGGCCCCGCGCC-3' (FRAG. NO:2243) (SEQ ID NO:11625)  
 5'-GGGGCCCCGCGC-3' (FRAG. NO:2244) (SEQ ID NO:11626)  
 5'-GGGGCCCCGCG-3' (FRAG. NO:2245) (SEQ ID NO:11627)  
 5'-GGGGCCCCG-3' (FRAG. NO:2246) (SEQ ID NO:11628)  
 5'-GGGGCCCC-3' (FRAG. NO:2247) (SEQ ID NO:11629)  
 5'-GGGCCCCGCGCCCGCC-3' (FRAG. NO:2248) (SEQ ID NO:11630)  
 5'-GGCCCCGCGCCCGCC-3' (FRAG. NO:2249) (SEQ ID NO:11631)  
 5'-GCCCCGCGCCCGCC-3' (FRAG. NO:2250) (SEQ ID NO:11632)  
 5'-CCCCGCGCCCGCC-3' (FRAG. NO:2251) (SEQ ID NO:11633)  
 5'-CCCGCGCCCGCC-3' (FRAG. NO:2252) (SEQ ID NO:11634)  
 5'-CCGCGCCCGCC-3' (FRAG. NO:2253) (SEQ ID NO:11635)  
 5'-CGCGCCCGCC-3' (FRAG. NO:2254) (SEQ ID NO:11636)  
 5'-GCGCGCCCGCC-3' (FRAG. NO:2255) (SEQ ID NO:11637)  
 5'-CGCCCGCC-3' (FRAG. NO:2256) (SEQ ID NO:11638)  
 5'-GCCCGCC-3' (FRAG. NO:2257) (SEQ ID NO:11639)  
 5'-GGGGCGCGGGGCGCGGG-3' (FRAG. NO:2258) (SEQ ID NO:11640)  
 5'-GGCGGGGCGGCGGCGGGCCCGG-3' (FRAG. NO:2259) (SEQ ID NO:11641)  
 5'-GGCGGTCGCGGTCGCCCCBGTGCGGCTCGCGC-3' (FRAG. NO:2260) (SEQ ID NO:11642)  
 5'-GCGCGGGCBBCBGCBBGCGGGCGCG-3' (FRAG. NO:2261) (SEQ ID NO:11643)  
 5'-GCGCBGCGGGCCCTGCGCGGGC-3' (FRAG. NO:2262) (SEQ ID NO:11644)  
 5'-GGGCGGGGTGGGCTGCCCTGCGGCCGCC-3' (FRAG. NO:2263) (SEQ ID NO:11645)  
 5'-GGGCTGCTGCGCGGCGGCTCCGGCGA-3' (FRAG. NO:2264) (SEQ ID NO:11646)  
 5'-CTCCCGGGCGGGCGGGCGCGGG-3' (FRAG. NO:2265) (SEQ ID NO:11647)  
 5'-GGGCTGCGCGGTCCGGGCCCCCTTGGCGGCG-3' (FRAG. NO:2266) (SEQ ID NO:11648)  
 5'-GCGCTCGCGCGCTGCCG-3' (FRAG. NO:2267) (SEQ ID NO:11649)  
 5'-GCGCGCTTGGCTTGTGCGGC-3' (FRAG. NO:2268) (SEQ ID NO:11650)  
 5'-GCTGCTCCBCGCTGG-3' (FRAG. NO:2269) (SEQ ID NO:11651)  
 5'-GCCGGBGGCCGGCCBGGTCCCGCG-3' (FRAG. NO:2270) (SEQ ID NO:11652)  
 5'-CCCGCGCGCGCBGGBGGCGGGTGGG-3' (FRAG. NO:2271) (SEQ ID NO:11653)  
 5'-GTCTCTCCCGCCCCCGCGCGC-3' (FRAG. NO:2272) (SEQ ID NO:11654)  
 5'-GGGCGTCCGCTCCGGGCGGTCGGG-3' (FRAG. NO:2273) (SEQ ID NO:11655)  
 5'-GCGGGACGCGCGGCTCTGGCGTCGGC-3' (FRAG. NO:2274) (SEQ ID NO:11656)

**Bradykinin Receptor Nucleic Acids and Antisense Oligonucleotide Fragments**

- 5'-GGTGBCBTTG BGCBTGTCGG CGCGTCCCG TTBBGBGTGG GCCCGCCAGC CCAGCCACTC CACTTGGGGG CGGGTGGCCA  
 GCACGAACAG CACCCAGAGG AAGGGGGGCG GCCCAGAAGG GCAGCCCGCA GGCCAGGATC AGGTCTGCTG CGGCCGGAGA

5 TAATGGCATT CACCACGCGG CGGCCAGCG CACGCCGCGC ATCCGGCCCG GGTCTGACC TGCAGCCCC GTCTCCTTGG  
 CATTCTGGG CCCCAGTCACT TCTCTCCCT GCCCCCTTG CTGGGGCAGG GACGGGGTG BCBTTGBGCB TGTGCGGCGG  
 GTCCCGTTBB GBGTGGGCCC GCCAGCCCAG CCACTCCACT TGGGGGCGGG TGGCCAGCAC GAACAGCACC CAGAGGAAGG  
 GGGGCGGCCC AGAAGGGCAG CCCGAGGCC AGGATCAGGT CTGCTGCGGC CGGAGATAAT GGCATTCAAC ACGCGGCGGC  
 10 CCAGCGCACG CCGCGCATCC GGGCCGGGTT CTGACCTGCA GCGCCGCTCT CTTTGGCATT CCTGGGCCCC AGTCACTCCT  
 CTCCTGCCCC CCGTGTCTGG GGCAGGGACG GCCGTGTGTT CBGTGGTGGT GCGCGTTTGB GGTBTGGGCG TCCBCCBBTT  
 CCTTTTCTC CTGTGTTTCC GTTCTCTTG CCGTCTGTGG TT CAGATTCAACA AACTGCAGGA CTGGGCAGGG AGCAGACAGT  
 GAGCAAAACG CAGCAGGGCT GCTGTGAATT TGTGAAGGA TTGAGGGACA GTTGCTTTTC AGCATGGGCC CAGGAATGCC  
 AAGGAGACAT GTATGCACGA CTTTGGGAAA TGAGTTGATG TCTCCGGTAA AACACCGGAG ACTAATTCCT GCCCTGCCCA  
 15 ATTTTGCAGG GAGCATGGCT GTGAGGATGG GGTGAACATG CGCACAGCCA AGGACTCCAA AATCACAACA CCAATTACTGT  
 TCTTATTGTC TGCCACACCT GAGCCAGCCT GCTCCTTCCC AGGAGTGGAG GAGGCCTGGG GGGAGGGAGA GGAGTGACTG  
 AGCTTCCCCT CCGTGTGTTT TCCGTCCCTG CCCCAGCAAG ACAACTTAGA TCTCCAGGAG AACTGCCATC CAGCTTTGGT  
 GCAATGGCTG ACCAGTGTCT AGTGTGTTG CCGTGGGTTT CTTTAATCTA TTCAGCTAGA ACTTTGAAGG CAATTTCTTT  
 GCATTAATAA AGGTTAAGCC CTGAGGGGTC CTGATAACA ACCTGGAGAC CAGGATTTTA TGGCTCCCCT CACTGATGGA  
 20 CAAGGAGGTC TGTGCCAAAG AAGAATCCAA TAAGCACATA TTGAGCACTT GCTGTATATG CAGTATTGAG CACTGTAGGC  
 AAGACCCAAG AAAGAGAAGG AGCCATCTCC ATCTGAAGG AACTCAAAGA CTCAAGTGGG AACGACTGGG CACTGCCACC  
 ACCAGAAAGC GTTTCGACGA CAGGTCGAG CAGGGTGATG TGGTGATAT GGACAGCAGA AGGGGGAGAC CAAGTTTCCA  
 GCTCAACCAA TAACTATTGC ACAACCACCT GTCCCTGCCT CAGTTCCTTT TTAATGAACA TGAAGTCGTT GTGAGGGTTA  
 AAGGCAGTAA CAGGTATAAA GTACTTAGAA AAGCAAAGGG TGCTACGTAC ATGTGAGGCA TCATTACGCA GACGTAACCTG  
 25 GGATGTGTTT ACTATAAGGA AAAGACACTG AGGTCTAGAA ATAGTCCGT GGAGCAGAAT CAGTATTGGG AGCCGGTGGC  
 GGTATGAGTC ACCAGTGTCT GGCACACAGT AGGTGCTCAT TGGCTCCCTT CCACCTGTCA TTCCACCACC CTTGAGGCC  
 CAACCGCCAC ACACACAGGA GCATTTGGAG AGAAGGCCAT GTCTTCAAAG TCTGATTTGT GATGAGGCAG AGGAAGATAT  
 TTCTAATCGG TCTTGCCCAAG AGGATCACAG TGCTGAGACC CCCCACCACC AGCCGGTACC TGGGAAGGGG GAGAGTGCAG  
 GCCTGCTCAG GGACTGTTCC TGTCTCAGCA ACCAAGGGAT TGTTCTGTC AATCAATGGT TTATTGGAAG TTTGGCCAGT  
 30 ATGAGCCCTA GAAGAGTGTG AAAAGGAATG AGAATGGTGT TACCATCGG CAGTGCCAGG GCAGCACTCA TTGAGTTGAT  
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 CCTGGAGAGG CTAGAACCAA GAAGGGCTAG AACCTGGAGG GGCTAGAACCT TAGAGAAGCT AAAACCTGAG CTAGAAGCTG  
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 35 CTAGAACCTG GAGGGCTAGA ACCTAGAAGG GCTAGAACCT GGAGGGCTGG AATCTGGAGA GCTAGAACCT GGAGGGCTAG  
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 CAGGTAGAAA CTTGGCAAGC TAGAACCTGG AGGGAATGAA CTTGGAGGGC TAGAACCTGG AGAATGAGAA AATTTACAT  
 GGCAAAGAGC CCATAAATCC TGACCAATCC AACTCTGAAT TTTAAAGCAA AAGCGTGAAG AAAAAGATTCT CCTCTTACC  
 40 CCAACCCAC TCTTTTTTCC CACCACCCAC TCTCTCTGC CTAGTAAGT ATCTGGAGGA AGAAAACAGG TGAAAGAAGA  
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 CAATGGCCAT GTGGGGATCC ACACCTGGTC TGAGGGGCAA CTGAGTCTGC GGGAGAAGAG CGGCCCTATG CATGGTGTAG  
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 45 CGAGAAAAAT ATGTAACAT GTGTCTTTTCT TGTAGAGCAT AATAAATGGA TGAGGTTTTT GCAAAAAAAG AAAAAAAGG  
 AAATGATAGA CCGTCAATAA TTGTGTAAT CTTTTTTAA ATGAATGCTT TAAGCCGGGT GCAGTGCTC ACATCTGTAA  
 TCCAGCACT TTGGAGCCGA GCGGGTGGAT TGTGTGAGGT CAGGAGTTCG AGACCAACCT GGCCAACATG GCAAAACCTC  
 ACTCTTACC AAAAATACAA AAATTAGCCA GGCATGGTGG CAGGCACCTG TGATCCAGC TACTCAGGAG GCTGAGACAG  
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 50 GACTCCGTCT CAAAAAAGG AAAAAAATAC GCTTCAACA CATGATCTCT CACCAGTGT GAATTTTCTT  
 TCTATGAGC CAGGAGGGCC TCTCAGAGAG GAAAGTCTCT AGGTCTCTCT TTCCCTCTGC AAACCTCCTG CCTTGAAGGT  
 TCAGAAAGGAC TGTGCGTGCT CGTTGCATCC TTTGCAAGTG TCCAAACCTT GATCCAGCT GTGCTTAGGG GTTCTTGCAA  
 ACCTTTCCA GGTGTTAATT ACCTCCACT TCAATTTCTG TTTACCAACT CAGCTTTTTG TTTAGTGTG TTTGAATTCC  
 CTGAAGTAC CGTTGTCTGA TCTCCACCTC CCAACTGAAT TAGGGGAGCT GGGCTTCTGG AAACCCAGGT GCGGGGTGTT  
 GCAGAGTGGC TGAAAGCTGG GATGTGGCAG ATCCGTGGCT ACATTCATGC ACACACACAC ACCCAGATAC CCACACATGC  
 55 ACACACACAC ACACACCCG ACTCACACAC TTGGACATGC ATAGACCACA GCTTTCCACA CCCTTCCATG ACAGGGGTGA  
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 60 GGGGACAGTA GGGAGCCCTG GGCTGAGAAC TTGACAGCAC CTTGTAATTG GTAAGCCAAG CCCGAAGGGA CTGGAATAAT  
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 65 TCAGGTTTAC CCTCTAAACT CCTCTGGAAT CCAGTCTCTC AGTCTCCATC ATCCAGGTC GAAGCTAATG GGCTAACTGG  
 TCCTTGCTTC CACTCTACCC CCACTGCACT OCTGACTTCC TGAGCAGCAG CCAGGGCCCTA ATCGATATTG ACACCAAGCG  
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 45 GGGCAGGGG TGCTCCAGCC GCCTCACCTC TGCTGGGAGG ACAAAGTCTC CCAGCACAGA GGGAGGGAGG GAGGCAGGC  
 AGCGGGGAGA AGTTCCCTG TGTCGTGGG GAGTT -3' (FRAG. NO:2275) (SEQ ID NO:11820)  
 5'- GCCCTTCAA GATGAGCTGT TCCCGCCGCC ACTCCAGCTC TGGCTTCTGG GCTCCGAGGA GGGGTGGGA CGGTGGGGAC  
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 50 AAGTTTCCCT GTGGTCTGG GGAGTT-3' (FRAG. NO:2275) (SEQ ID NO:11819)  
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 70 GTCTTCTGCC TGCACAAGAG CAGCTGCACG GTGGCAGAGA TCTACCTGGG GAACCTGGCC GCAGCAGAC TGATCTTGGC  
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 ATGCCATTAT CTCCATGAAC CTGTACAGCA GCATCTGTTT CTGATGCTG GTGAGCATCG ACCGCTACCT GGCCCTGGTG  
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 75 GCTACCCATC CCTCATCTGG GAAGTGTTCA CCAACATGCT CTGAATGTC GTGGGCTTCC TGCTGCCCT GAGTGTATC

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 5'- TGATCCTATC ACAACCTGAG AGTAGTTTT ACTCCATTTA CAGGTGAGGT CATTGTGGTT CAAGGACGTT AAGTAACTTC  
 10 CCCAGCTCAG ACGGCTTATA AGTAAGGCAG CCAGGATGTG AACCCAGTAG GACTATCTGG CTGCAAAGTC CCCACCCTCC  
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 65 GAACTCAAAG ACTCAAGTGG GAACGACTGG CACTGCCACC ACCAGAAAGC TGTCGACGA GACGGTGCAG CAGGGTGTCTG  
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 ATAGCTCCGT GGAGCAGAAT CAGTATTGGG AGCCGGTGGC GGTGTGAAGC ACCAGTGTCT GGCACACAGT AGGTGCTCAT  
 TGCTCCCTT CCACCTGTCA TCCCCACC CCTGAGGGCC CAACCGCCAC ACACACAGGA GCATTTGGAG AGAAGGCCAT  
 GTCTTCAAAG TCTGATTTG GATGAGGCAG AGGAAGATAT TTCTAATCGG TCTTGCCAG AGGATCACAG TGCTGAGACC  
 25 CCCCACCACC AGCCGGTACC TGGGAAGGGG GAGAGTCGAG CCGTGTCTGAG GGACTGTTCC TGCTCAGCA ACCAAGGGAT  
 TGTTCTGTG AATCAATGGT TTATTGGAAG GTGGCCAGT ATGAGCCCTA GAAGAGTGTG AAAAGGAATG GCAATGGTGT  
 TCACCATCGG CAGTGCCAGG GCAGCACTCA TTCATTTGAT AAATGAATAT TTATTAGCTG GTTGGAGAGC TAGAACCTGG  
 AGAGCTAGAA CCTGGAGAAC TAGAACCTGG AGGGCTAGAA CCTGGAGAGG CTAGAACCAA GAAGGGCTAG AACCTGGAGG  
 GGCTAGAAC TAGAGAAGCT AAAACCTGAG CTAGAAGCTG GAGGACTAGA ACCTGGAGGG CTGGAATCTG AAGGGCTAGA  
 30 ACCTGGAGGG CTGGAATCTG GAGAGCTAGA ACCTGGAGGG CTAGAACCTG GAGGGCTAGA ACCTAGAAGG GCTAGAACCT  
 GGAGGGCTGG AATCTGGAGA GCTAGAACCT GGAGGGCTAG AACCTGGAGG GCTAGAACCT AGAAGGGGTA GAACCTGGAG  
 GGCTAGAACC TGGCAGGTTA GAACCTGAA GGGCTAGAAC CTGGAAGGCC AGAACCTGGA GGGCTAGAAC CTGGAAGGGC  
 TAGAACCTGT AGAGCTAGAA CATGGAGAGC TAGAACCCGG CAGGCTAGAA CCTGGCAAGC TAGAACCTGG AGGGAATGAA  
 CCTGGAGGGC TAGAACCTGG AGAATGAGAA AAATTTACAT GGCAAAGAGC CCATAAATCC TGACCAATCC AACTCTGAAT  
 35 TTTAAAGCAA AAGCGTGAAA AAAAAGATTG CCTCTTACC CCCAACCCAC TCTTTTTC CACCAACCC TCTCTCTGC  
 CTCAAGAT ATCTGGAGGA AGAAAACAGG TGAAGAAGA AGTAAAGAAC ATTAGTATT AGTATTAGAA TGAAGCTAAA  
 CTGTGCCACA CATGGTGAAT GAAAAAAGG TGTGTTTGT CACACAGGGC AGTCATTAG CACCAGAGCA  
 CGTGATGGTC TGAGACTCTC TTAGGAGCAG AGCTCTGCCG CAATGGCCAT GTGGGGATCC ACACCTGGTC TGAGGGGCAA  
 CTGAGTCTGC GGGAGAAGAG CGGCCCTATG CATGGTGTAG ATGCCCTGAT AAAGAACATC TGTCCTGTGA AAGACTCAAT  
 40 GAGCTGTTAT GTGTAAACA GGAAGCATTT CATCTAGAAA CGAGAATAATC ATGTAAACAT GTGTCTTTC TGTAAGCAT  
 AATAAATGGA TGAGGTTTTT GCAAAAAAAA AAAAAAAA -3' (FRAQ. NO: ) (SEQ ID NO 2431)  
 5'-GGTGBCBTTTGGCBTGTGCGGCGC-3' (FRAG. NO:2276) (SEQ ID NO:11658)  
 5'-GGTCCCGTTBBGBGTGGGCC-3' (FRAG. NO:2277) (SEQ ID NO:11659)  
 5'-GCCAGCCAGCCACTCCACTTGGGGGC-3' (FRAG. NO:2278) (SEQ ID NO:11660)  
 45 5'-GGGTGGCCAGCACGAACAGCACCCAGAGGAAGGGGGC-3' (FRAG. NO:2279) (SEQ ID NO:11661)  
 5'-GGCCAGAAAGGGCAGCCCGCAGGCCAGGATCAGGTCTGCTGCGGCC-3' (FRAG. NO:2280) (SEQ ID NO:11662)  
 5'-GGAGATAATGGCATTACACACGCGGC-3' (FRAG. NO:2281) (SEQ ID NO:11663)  
 5'-GGCCAGCGCAGCCCGCGCATCCGGGCC-3' (FRAG. NO:2282) (SEQ ID NO:11664)  
 5'-GGGTCTGACCTGCAGCCCCC-3' (FRAG. NO:2283) (SEQ ID NO:11665)  
 50 5'-GTCTCCTTGGCATTCCTGGGGCC-3' (FRAG. NO:2284) (SEQ ID NO:11666)  
 5'-CAGTCACTCTCTCCCTGCCGCC-3' (FRAG. NO:2285) (SEQ ID NO:11667)  
 5'-CTTGCTGGGCGAGGACGG-3' (FRAG. NO:2286) (SEQ ID NO:11668)  
 5'-GGTGBCBTTTGGCBTGTGCGGCGC-3' (FRAG. NO:2287) (SEQ ID NO:11669)  
 5'-GGTCCCGTTBBGBGTGGGCC-3' (FRAG. NO:2288) (SEQ ID NO:11670)  
 55 5'-GCCAGCCAGCCACTCCACTTGGGGGC-3' (FRAG. NO:2289) (SEQ ID NO:11671)  
 5'-GGGTGGCCAGCACGAACAGCACCCAGAGGAAGGGGGC-3' (FRAG. NO:2290) (SEQ ID NO:11672)  
 5'-GGCCAGAAAGGGCAGCCCGCAGGCCAGGATCAGGTCTGCTGCGGCC-3' (FRAG. NO:2291) (SEQ ID NO:11673)  
 5'-GGAGATAATGGCATTACACACGCGGC-3' (FRAG. NO:2292) (SEQ ID NO:11674)  
 5'-GGCCAGCGCAGCCCGCGCATCCGGGCC-3' (FRAG. NO:2293) (SEQ ID NO:11675)  
 60 5'-GGGTCTGACCTGCAGCCCCC-3' (FRAG. NO:2294) (SEQ ID NO:11676)  
 5'-GTCTCCTTGGCATTCCTGGGGCC-3' (FRAG. NO:2295) (SEQ ID NO:11677)  
 5'-CAGTCACTCTCTCCCTGCCGCC-3' (FRAG. NO:2296) (SEQ ID NO:11678)  
 5'-CTTGCTGGGCGAGGACGG-3' (FRAG. NO:2297) (SEQ ID NO:11679)  
 5'-CCGTGTTGTGCBTGGTGCTG-3' (FRAG. NO:2298) (SEQ ID NO:11680)  
 65 5'-CCCGTTTBBGGTBTGGC-3' (FRAG. NO:2299) (SEQ ID NO:11681)  
 5'-GCTCCBCCBTTTCCCTTTCTCC-3' (FRAG. NO:2300) (SEQ ID NO:11682)  
 5'-TTGTTTTCCGTTTCTCTTG-3' (FRAG. NO:2301) (SEQ ID NO:11683)  
 5'-CCGTCTGTGGTT-3' (FRAG. NO:2302) (SEQ ID NO:11684)

**B2 Adrenergic Receptor Kinase Nucleic Acids and Antisense Oligonucleotide Fragments**

70 5'-GCCCGCCCG CCAAGATGGC GGACCTGGAG CGGGTCTGG CCGACGTGAG CTACCTGATG GCCATGGAGA AGAGCAAGGC  
 CACGCCGGCC GCGCGGCCA GCAAGAAGAT ACTGCTGCC GAGCCAGCA TCCGCAGTGT CATGCAGAA TACCTGGAGG  
 ACCGGGGCGA GGTGACCTT GAGAAGATCT TTCCAGAA GCTGGGGTAC CTGCTCTCC GAGACTTCTG CTTGAACCA  
 CTGAGGAGG CGAGGCCCTT GGTGAATTC TATGAGGAGA TCAAGAAGTA CGAGAAGCTG GAGACGGAGG AGGAGCTGTG  
 GGGCCGAGC CCGGAGATCT TCGACTATA CATATGAAG GAGCTGCTGG CCGTCTCGCA TCCCTTCTG AAGAGTGCCA  
 75 CTGAGCATGT CCAAGGCCAC CTGGGGAAGA AGCAGGTGCC TCCGATCTC TTCCAGCCAT ACATCGAAGA GATTGTGCA

AACCTCCGAG GGGACGTGTT CCAGAAATTC ATTGAGAGCG ATAAGTTCAC ACGGTTTTGC CAGTGGAAGA ATGTGGAGCT  
CAACATCCAC CTGACCATGA ATGACTTCAG CGTGCATCGC ATCATTGGGC GCGGGGGGCTT TGGCGAGGTC TATGGGTGCC  
GGAAGGCTGA CACAGGCAAG ATGTACGCCA TGAAGTGCTT GGACAAAAG CCGCATCAAGA TGAAGCAGGG GGAGACCCCTG  
GCCCTGAAACG AGCGCATCAT GCTCTCGCTC GTCAGCACTG GGGACTGCCC ATTCATTGTC TGCATGTTCAT ACGCGTTCCA  
5 CACGCCAGAC AAGCTCAGCT TCATCTGGA CCTCATGAAC GGTGGGGACC TGCACTACCA CCTCTCCAG CACGGGGTCT  
TCTCAGAGGC TGACATGCGC TTCTATGCGG CCGAGATCAT CTTGGGCGCTG GAGCACATGC ACAACCGCTT CGTGGTCTAC  
CGGGACCTGA AGCCAGCCAA CATCCTTCTG GACGAGCATG GCCACGTGCG GATCTCGGAC CTGGGCGCTGG CCTGTGACTT  
CTCCAAGAAG AAGCCCATG CCAGCGTGGG CACCCACGGG TACATGGCTC CGGAGGTCTT GCAGAAGGGC GTGGCCTACG  
ACAGCAGTGC CGACTGGTTC TCTCTGGGGT GCATGCTCTT CAAGTTGCTG CGGGGGCACA GCCCTTCCG GCAGCACAAG  
10 ACCAAAGACA AGCATGAGAT CGACCCGATG ACGCTGACGA TGGCCGTGGA GCTGCCCGAC TCCTTCTCCC CTGAACACG  
CTCCCTGCTG GAGGGGTGTC TGCAGAGGGA TGTCAACCGG AGATTGGGCT GCCTGGGCGG AGGGGCTCAG GAGGTGAAAG  
AGAGCCCTTT TTTCGCTCC CTGGAGTGGC AGATGGTCTT CTTGCAGAAG TACCCTCCCC CGCTGATCCC CCCACGAGGG  
GAGGTGAACG CGGCCGACGC CTTCGACATT GGCTCCTTCG ATGAGGAGGA CACAAAAGGA ATCAAGTTAC TGGACAGTGA  
15 TCAGGAGCTC TACCCGCACT TCCCTCTCAC CATCTCGGAG CGGTGGCGAG AGGAGGTGCG AGAGACTGTC TCCAGACCA  
TCAACGCTGA GACAGACCGG CTGGAGGCTC GCAAGAAAGC CAAGAACAAG CAGCTGGGCC ATGAGGAAGA CTACGCCCTG  
GGCAAGGACT GCATCATGCA TGGCTACATG TCCAAGATGG GCAACCCCTT CCTGACCCAG TGGCAGCGGC GGTACTTCTA  
CCTGTTCCCT AACCGCTCG AGTGGCGGG CGAGGGCGAG GCCCGCAGA GCCTGCTGAC CATGGAGGAG ATCCAGTCCG  
TGGAGGAGAC GCAGATCAAG GAGCGCAAGT GCCTGTCTCT CAAGATCCGC GGTGGGAAAC AGTTCAATTT AGTAGTGCAT  
20 AGCGACCCCT AGCTGGTGCA GTGGAAGAAG GAGCTGCGCG ACGCTACCG CGAGGCCAG CAGCTGGTGC AGCGGGTGCC  
CAAGATGAAG AACAAAGCCG GCTCGCCCGT GGTGGAGCTG AGCAAGGTGC CGCTGGTCCA GCGCGGCGAT GCCAACGGCC  
TCTGACCCCG CCACCCGCTT CCAGGAAGCT ACCTGGAGGA GGTGAGTCTT AGCGGATGAG TAGGAGTTGT CACCGGAGGA  
AGGTACACAG AAGGGCTTCC AGGCCAGGA AACAGCAGAG GCACAGAAGT GAGAATGGGT GGGTGAGTTG GTGGGAAAC  
TCCAGGTGCA GAGGATGGTA GCGAAAACAA CTGGAGCATT AAGTTCCAA TCCCTCAAAGA TCTTGACTTG CAGATTAAGG  
25 AGTTTGTTC CTAATCTGC TTGGGCGAGA GTGTGGTGAG TCCTAGAGAC CCCTCTAGGT CTCTCTCTC AGTAGCCCCA  
GAAGGCTGG AGAGCTGCTT CTGGGTGCCA AGCAGCAGT GACTCCATCA GATCTAGATT TGGGAAAGC ATCCCTGGTC  
AGGGCCTGCA TCAGGGCAGT GGCTGGCCAT GAGGACCTG AGAAGTAGAC AGATTACCG AGATTCTCAG GAGGCCAGAC  
AGGAGACTAT GGTGACAAAT TAGATTAGAG AAGGGGAGAG AATGAAGGAG CAGTTGGGGT AAAAGAAAAC TGAGGCTGAC  
ATGGGTATAT GGTGCGCAG TGACTACCA CCCACTGAGA GGAGAACCTC ACAAGCTCTG ACATGCTCTG GTTCCAGTT  
30 CTGTTGGGCG TGATCCAAGA TGGTAGCTTA GAGGTGCACA GAGTGGGGG CCTTGCTTG CAAAAGGATG CTGGCTGCTG  
GCCACAGCA TGGTAATGAG ATTTGAGCTT TATGTGCCA GGGCTGGGAG GAGGGTCTCT TCACTTTGAA AGCAAAGAGA  
GGCTCTAGAG AGGGGCTAGT TGAGATAGGA ATGCTGCCTT GAGACACCTG GCTTTCCTCA CTCTGGGTGG CTCTCAGCAG  
GGTGGGTTTC CCCTGCCAGT CAGCACTGAA CCTCTGTGCG TCTCCGGCTG GGAGAGTTTT TACCCTAAT ACATGTGGAA  
CCATCTGAA GGAACATCTG GATGGGATGG GGTACAGGGA AGGGAGCTGC CAAGAGTGCT GGCCAGGGAC CTGGGTCTAT  
35 GAGCTGGTTG GGGGGTGGGG TTGGGTGCA GGTACTTGAT CCTGAGTGGG CCTTCTGCGG CCAGGATTGG TTCTAGAGTA  
GGAGGGGTGG GATCGGGGAT GGGGGAAGCC TGTAACTGCG CTGCAAGTTG CAGGTCCCAG GTTCTGGGTG ACCTACTAAG  
GATCTGGGT CACGTGTGGG TCCCAGTTA GAGTCCCTAG TCCTGAGTCC GTGTCCACAG TTCTGGGTGT TAGTCTAGG  
ACAGTGATCT GGAGTTGACA GTCCAATCTA GGTCTGAGTC CTGACCCCAA GTCTAGAGTT CAGGGTCTAG GTAGTAGCCT  
AGGGTCAGAA TCAAGGTTGG GGTGAGTAAC CAGGATGGGA TCGAGGTCTAT GGTCCAAAAT CTGGATCTGG GGACCTGTTG  
40 GGGGTCTGAG CTAAGTGTG CAGTCTGGT ATGGCGTTGG AGACCCAGGG CTGTGATCTG AGGTCTAAGT TAGAGTCTCA  
GGTGGTGGG CTAAGGTTGA GTCTGGGGTC CTGTTTGGAG TGTGGTGTCA GTTCGTGGAC GGTCTGAGG TCAGGCGGAGT  
CCGGGGTTAT AGCCAGGGTC TGAGATGAAA GTCCAGATG GTGTTCAAG GTCTGAATCT GTGTCTTGGT GAGCGTCCAG  
GTTCCCTGTG ATCAGTTTG GTGTCAAGGC TGCGGCCCGA CTGGGAGGCC TGGGATCCAG AGATGTGACC CGAGGTTGTG  
GTCAGAGAAT GGGTCTCGGG TCGTCTCGT GCCGGGTCCC TGTGTTGTC CAGGCCGGG TCTCCGTCCA CACGCGGAGG  
45 CCGAGGTCAC GGCCAGGGTC TGAGCCCGCG GTGCGAGGTC TGGTTCGGGG TCAGATTCCG CCGCGGCTCC AGGGGGCGCC  
GTGCGCGCCC GGCTCGGCC CTGCGGGGCT CGCTGCGGTT GTGCGCGGCA GCGGGGGCCG GAGGCGGCGG CGGTCCGGG  
GGCGCGGGCC GGGCGGCGG GGGCGGCGG CCGGACTGCG AGTCCCGCG GAGCGGAGC GCGAAGCGCG GGGCGGGGCC  
CGGAGCCGGG CAGGATGGGG GTGCGCGGCG GCGCGCGGCG CCGCGGGCGG CCGAGCAGGG CCGAGCAGGG GCGCGGGCGG  
CGTGGCGGCC CGAGGCGGAG CGAGCGCGG CCGGGCGGG CCGAGCGCG AGCGAGCAGG AGCGGCGGCG GCGCGGGCGG  
CGGCGGGAGG AGGCAGCGCC GCGGCCAAGA TGCGCGACCT GGAGCGGCTG CTGGCCGACG TGAGCTACCT GATGCGCATG  
50 GAGAAGAGCA AGGCCACGCC GCGCGCGCG GCCAGCAAGA AGATACTGCT GCCCGAGCCC AGGTGAGGAG AAGCT-3' (FRAG.  
NO: ) (SEQ ID NO: 11799)  
5'-CCAGGAAGCT ACCTGGAGGA GGTGAGTCTT AGCGGATGAG TAGGAGTTGT CCACGGAGGA AGGTACACAG AAGGGCTTCC  
AGGCCCAGGA AACAGCAGAG GCACAGAAGT GAGAATGGGT GGTGAGTTG GTGGGAAAC TCCAGGTGCA GAGGATGGTA  
GCGAAAACAA CTGGAGCATT AAGTTCCAA TCTTCAAGT CAGATTAAGG AGTTTGTTC CTAATCTGC CTAATCTGC  
55 TTGGGCGAGA GTGTGGTGAG TCCTAGAGAC CCCTCTAGGT CTCTCTCTC AGTAGCCCCA GAAGGCCCTGG AGAGCTGCTT  
CTGGGTGCCA AGCAGGCAGT GACTCCATCA GATCTAGATT TGGGAAAGC ATCCCTGGTC AGGGCCTGCA TCAGGGCAGT  
GGCTGGCCAT GAGGACCCCTG AGAAGTAGAC AGATTACCG AGATTCTCAG GAGGCCAGAC AGGAGACTAT GGTGACAAAT  
TAGATTAGAG AAGGGGAGAG AATGAAGGAG CAGTTGGGGT AAAAGAAAAC TGAGGCTGAC ATGGGTATAT GGTGGCGAG  
TGACTACCA CCCACTGAGA GGAGAACCCT ACAAGCTCTG ACATGCTCTG GTTCCAGGTT CTGTTGGGGC TGATCCAAGA  
60 TGGTAGCCTA GAGGTGCACA GAGATGGGGG CTTGCTTTG CAAAAGGATG CTGGCTGCTG GCCACAGCA TGGTAATGAG  
ATTTGAGCTT TATGTGCCA GGGCTGGGAG GAGGCTCTG TCACCTTGAA AGCAAAGAGA GGCTCTAGAG AGGGCATGT  
TGAGATAGGA ATGTGCTT GAGACACCTG GCTTTCCTCA CTCTGAGTGG CTCTCAGCAG GGTGGGTTTC CCCTGCCAGG  
CAGCACTGAA CCTCTGTGCG CTTCGGGCTG GGAGAGTTTT TACCCTAAT ACATGTGGAA CCATCCTGAA GGAACATCTG  
GATGGGATGG GGTACAGGGA AGGGAGCTGC CAAGAGTGTG GGCAGGGGAC CTGGGTCTAT GAGCTGGTGT GGGGGTGGGG  
65 TTGGGTGCG GGTACTTGAT CCTGAGTGGG CACTTCTGCG CCAGGATGTT TTCTAGAGTA GGAGGGGTGG GATCGGGAT  
GGGGGAAGCC TGTAACCTGCG CTGCAAGTTG CAGGTCCCAG GTTCTGGGTG ACCTACTAAG GATTCTGGGT CCAAGTCTGG  
TCCAGGTTA GACGTCTAG TCCTGAGTCC GTGTCCACAG TCTTGGGTGT TGAGTCTAGG ACAGTGATCT GGAGTTGACA  
TGCCAATCTA GGTCTGAGT CTGACCCCAA GTCTAGAGTT CAGGGTCATG GTAGTAGCCT AGGGTCAGAA TCAAGGTTGG  
GGTCACTAAC CAGGATGGGA TCGAGGTCA GTTCCAAAAT CTGGATCTGG GGAGCTGTTG GGGGTCTGAG GGTGCTGCG  
70 CAGTCTGGGT ATGGCGTTGG AGACCCAGGG CTGTGATCTG AGGTGATGTT TAGAGTCTCA GGTGGTGGG CAAGGTTTGA  
GTCTGGGGTC CTGTTTGGAG TCTGGTGTCA GGTCTGGGAC TGCGTCCAAG GTCAGGGAGT CCGGGGTTAT AGCCAGGGTC  
TGAGATGAAA GTCCAGATG GTGTTCAAG GTTCTGAATCT GTGCTTGGT GAGCGTCCAG GTTCCCTGTG ATCAGGTTT  
GTGTCAGGGC TGCGGCCCGA CTGGGAGGCC TGGGATCAG AGATGTGACC CGAGGTTGTG GTCAGAGAA GGTGCTGGG  
TGTCTTCTGT GCCGGGTCCC TGTGCTGTT CAGGCCCGGG TCTCCGTCCA GCATCGAGGG CCGAGGTGAC GGGCAGGGTC  
75 TGAGCCCGCG GTGCGAGGTC TGGTTCGGGG TCAGATTCCG CCGCGGCTCC AGGGGGCGCC GTGCGCGGCC GGCTCGGCC

CTCGCGGGCT CGCTGGCGTT GTGCGCGGCA GCGCGGGCCG GAGGCGGCGG CGGCTCCGGG GCGCGGGGCC GGGCGGCGGC  
 GCGCGCGGCG CCCCGACTGC AGTCCCGGCG GGAGCGGAGC GCGAAGCGCG GGGCGGGGCC CGAGAGCCGC GCCATGGGGC  
 GCGCGCGCCT GTGAGCGGCG GCGAGCGGAG CCGCGGGCGC CGAGCAGGCG CAGGCGGGAG CGTCGGCGCC CGAGGCCGAG  
 CGAGCCGCGG CCGGCGCGG CCGAGCGCGG AGCGAGCAGG AGCGCGCGCG GCGGCGGGAG AGGCAAGCGC  
 5 GCGGCCAAGA TGGCGGACCT GGAGGCGGTG CTGGCCGACG TGAGCTACCT GATGGCCATG GAGAAGAGCA AGGCCACGCC  
 GCGCGCGCGC GCCAGCAAGA AGATACTGCT GCGCGAGCCC AGGTGAGGAG AAGCT-3' (FRAG. NO.:) (SEQ ID NO:11798)  
 5'-GCCGCGCGC CCAAGATGGC GGACCTGGAG GCGGTGCTGG CCGACGTGAG CTACCTGATG GCCATGGAGA AGAGCAAGGC  
 CACGCGGGCC GCGCGCGCCA GCAAGAAGAT ACTGCTGCC GAGCCAGCA TCCGAGTGT CATGCAGAAG TACCTGGAGG  
 10 ACCGGGGGCG GGTGACCTTT GAGAAGATCT TTTCCAGAA GCTGGGGTAC CTGCTCTTCC GAGACTTCTG CCTGAACCAC  
 CTGGAGGAGG CCGAGCCCTT GGTGGAATTC TATGAGGAGA TCAAGAAGTA CGAGAAGCTG GAGACGGAGT AGGAGCGTGT  
 GCGCCGCGAG CCGGAGATCT TCGACTCATA CATCATGAAG GAGCTGCTGG CCTGCTCGCA TCCCTTCTCG AAGAGTGCCA  
 CTGAGCATGT CCAAGGCCAC CTGGGGAAGA AGCAGGTGCC TCCGATCTC TTCCAGCCAT ACATCGAAGA GATTGTGCAA  
 AACCTCCGAG GAGACTGTGT CCAGAAATTC ATTGAGAGCG ATAAGTTCAC ACGTTTTCG CAGTGGAAGA ATGTGGAGCT  
 15 CAACATCCAC CTGACCATGA ATGACTTCAG CTGTGATCGC ATCATTGGGC GCGGGGGCTT TGGCGAGGTC TATGGGTGCC  
 GGAAGGCTGA CACAGGCAAG ATGTACGCCA TGAAGTGCCT GGACAAAAAG CGCATCAAGA TGAAGCAGGG GGAGACCCTG  
 GCCCTGAACG AGCGCATCAT GCTCTCGCTC GTCAGCACTG GGGACTGCC ATTCAATTGT TGCATGTCAT ACGCGTTCCA  
 CACGCCAGAG AAGCTCAGCT TCATCCTGGA CCTCATGAAC GGTGGGGACC TGCACTACCA CCTCTCCAG CACCGGGTCT  
 TCTCAGAGGC TGACATGCGC TTCTATGCGG CCGAGATCAT CCTGGGCTCG GAGCACATGC ACAACCGCTT CGTGGTCTAC  
 CCGGACCTGA AGCCAGCCAA CATCTTCTG GACGAGCATG GCCACGTGCG GATCTCGGAC CTGGGCTCG CCTGTGACTT  
 20 TCCCAAGAAG AAGCCCCATG CCAGCGTGGG CACCCACGGT TACATGGCTC CGGAGGTCTT GCAGAAGGCC GTGGCTACG  
 ACAGCATGAG CCGACTGGTC TCTCTGGGT GATGCTCTT CAAGTTGCTG CCGGGGACCA GCCCTTCCG CACGCAAG  
 ACCAAAGACA AGCATGAGAT CGACCGCATG ACGCTGACGA TGGCGTGGG GCTGCCCGAC TCCTTCTCCC CTGAACACG  
 CTCCTGCTG GAGGGGTTGC TGCAAGAGGA TGTCACCCG AGATTGGGT GCCTGGGCG AGGGGCTCAG GAGGTGAAAG  
 AGAGCCCTT TTTCCGCTCC CTGGACTGGC AGATGGTCTT CTTCGAGAAG TACCTCCCC CGCTGATCCC CCCACGAGG  
 25 GAGGTGAACG CCGCCGAGCG CTTCGACATT GGCTCCTTCG ATGAGGAGGA CACAAAAGGA ATCAAGTTAC TGGACAGTGA  
 TCAGGAGCTC TACCGCAACT TCCCTCTCAC CATCTCGGAG CCGTGGCAGC AGGAGGTGGC AGAGACTGTC TTCGACACCA  
 TCAACGCTGA GCAGAGCCG CTGGAGGCTC GCAAGAAAGC CAAGAACAAG CAGCTGGGCC ATGAGGAAGA CTACGCCCTG  
 GGCAAGGACT GCATCATGCA TGGTACATG TCCAAGATGG GCAACCCCTT CTGACCCAG TGGCAGCGGC GGTACTTCTA  
 CTGTTCCTCC AACCCGCTCG AGTGGCGGGG CGAGGGCGAG GCGCCGACGA GCCTGCTGAC CATGGAGGAG ATCCAGTCGG  
 30 TGAAGGAGAC GCAGATCAAG GAGCGCAAGT GCTGCTCTCT CAAGATCCGC GGTGGGAAAC AGTTCAATTT GCAGTGCAT  
 AGCGACCCTG AGCTGGTGCA GTGGAAGAA GAGTGCCTG ACGCTACCG CGAGGCCAG CAGCTGGTGC AGCGGGTGCC  
 CAAGATGAAG AACAAAGCCG GCTCGCCGT GGTGAGCTG AGCAAGGTGC CGTGTGTCCA GCGCGGCACT GCCAACGGCC  
 TCTGACCCGC CCACCCGCT-3' (FRAG. NO.:) (SEQ ID NO:11797)

#### **CCR-2 CC Chemokine Receptor Nucleic Acids and Antisense Oligonucleotide Fragments**

35 5'-CTTTGTGAAG AAGGAATTGG CAACACTGAA ACCTCCAGAA CAAAGGCTGT CACTAAGGTC CCGTGCCTT GATGGATTAT  
 AACTTGACC TGAGTGTGAC AACAGTGACC GACTACTACT ACCTGATAT CTCTCAAGC CCCTGTGAT CGGAACCTAT  
 TCAGACAAAT GGCAAGTTGC TCCTTGCTGT TTTTATTTG CTCTGTTTG TATTCACTCT TCTGGGAAAC AGCTGGTCA  
 TCCTGGTCTC TGTGGTCTGC AAGAAGCTGA GGAGCATCAC AGATGTATAC CTCTGAACC TGGCCTGTG TGACCTGCTT  
 TTTGTCTTCT CCTTCCCTT TCAGACCTAC TATCTGCTGG ACCAGTGGGT GTTTGGGACT GTAATGTGCA AAGTGGTGT  
 40 TGTCTTTTAT TACATTGGCT TCTACAGCAG CATGTTTTTC ATCACCCTCA TGAGTGTGGA CAGGTACCTG CAGTGTGTCC  
 ATGCCGTGTA TGGCCTAAAG GTGAGGACGA TCAGGATGGG CACAACGCTG TGCCTGGCAG TATGGCTAAC CGCATTATG  
 GCTACCATCC CATTGCTAGT GTTTTACCAA GTGGCCTCTG AAGATGGTGT TCTACAGTGT TATTCATTTT ACAATCAACA  
 GACTTTGAAG TTGAAGATCT TCACCAACTT CAAAATGAAC ATTTTAGGCT TGTGTATCCC ATTCACCATC TTTATGTTCT  
 GCTACATTAA AATCCTGCAC CAGCTGAAGA GGTGTCAAAA CCACAACAAG ACCAAGGCCA TCAGGTTGGT GCTGTTGTG  
 45 GTCATTGCAT CTTTACTTTT CTGGGTCCCA TTCAACGTGG TTTCTTCTCT CACTTCTTG CACAGTATGC ACATCTTGA  
 TGGATGTAGC ATAAGCCAAC AGCTGACTTA TGCCACCCAT GTACAGAAA TCATTTCCT TACTACTGC TGTGTGAACC  
 CTGTTATCTA TGCTTTTGT GGGGAGAAGT TCAAGAAACA CCTCTCAGAA ATATTTCAGA AAAGTTGCAG CCAAATCTTC  
 AACTACCTAG GAAGACAAAT GCCTAGGGAG AGCTGTGAAA AGTCACTATC CTGCCAGCAG CACTCTCCC GTTCTCCAG  
 CGTAGACTAC ATTTTGTGAG GATCAATGAA GACTAAATAT AAAAAACATT TTCTTGAATG GCATGCTAGT AGCAGTGAGC  
 50 AAAGGTGTGG GTGTGAAAGG TTTCCAAAAA AAGTTCAGCA TGAAGGATGC CGTGTGTGTT GTTGCCAACA CTGGAACAC  
 AATGACTGGA GACATAGTTG TGATGCTG GACAAACATC AAGCTGTGA TTGTGTTTAT TGATGATGTG GAACAAGTGG  
 TGGCTTTGAG GGATTCTGTA TGCCAAGTGG AAAAAAAGA TGTCTCCGA ATTCGACAGG TTATCA-3' (FRAG. NO.:) (SEQ ID  
 NO:11831)

#### **CCR-4 CC Chemokine Receptor Nucleic Acids and Antisense Oligonucleotide Fragments**

55 5'-TTTCATCTCT CCGGGCTTAT TTGCTGGTIT CTCCGAATGC GGGCCTTGTC TGGTTCACGC TGGATCCCA ACGCTAGAA  
 CAGTGCCTGG CACGCAAGTT GTCTTCTAT AAATATCGGA CTAATGATAT CTCTGTGATG GTAATACCCA CACGGTGTG  
 TGAGAATGAA TGAGTGATTC TGTGCAAGTT CTTAGTGATC TGTACAAAA AGTACTGGTC GCTAAATTAC TCTTATAATA  
 AAGCATACTT TTAGGATAAT AAAGCACTAT TCGCAATGT GTTACCGCTA TTATGAAAT ACTGAGCAAT ACATATCTAC  
 60 ATCTGATCAG TCTCCAGAAT TATGCCAAAT CCTACCTTCT TGTGAAAGTA TCTCTAATT ATCTGCACCT GACCTATGAG  
 ATGCTGTGAA TGTGCAAGTA TAGCTACATC CTCCGAAGGA AGGATCTTTA CTCCTTTTAC CTCTGTAATG GGTGCGTCT  
 GCTGAAAGCG CCGGGGAATG GCGGTTGGA AGCTTGGCCC TACTCCAGC ATTGCGCCT ACTGGTGGG TTAATCCAGC  
 AAGTCACTCC CCTTCCCTGG GCCTCAGTGT CTCTACTGTA GCATTTCCAG GTCTGGAATT CCATCCACT TAGCAAGGAT  
 GGACGCGCCA CAGAGAGACG CGTTCCTAGC CCGCGCTTCC CACTGTCTT CAGGCGCATC CCGCTTCCCT CAACTATAGG  
 65 AAATGCCTCT GGGAGGTCTT GTCCGGCTCC GGACTCACTA CCGACCACCC GCAAAACAGCA GGGTCCCCTG GGCTTCCCAA  
 GCCGCGCACC TCTCCGCCCC GCCCTGCGC CTCTCTTCTT CCGCTCTGCC CTCTTCCCTC ACCCGCCTT CTCCCTCCCC  
 GCCCCAGCGG CGCATGCGCC GCGCTCGGAG CGTGTTTTTA TAAAGTCCG GCCGCGGCCA GAAACTTCAG TTTGTTGGCT  
 GCGGCGCAGG GTAGCAAAAGT GACGCCGAGG GCTGAGTGC TCCAGTAGCC ACCGCATCTG GAGAACCAGC GGTATACATG  
 GAGGGGATCA GTGTAAGTCC AGTTTCAACC TGCTTTGTCA TAAATGTACA AACGTTTGAA CTTAGAGCGC AGCCCTCTC  
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#### CD-34 Nucleic Acids and Antisense Oligonucleotide Fragments

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 25 CGGCGGGAAG AGCGCGTCT GGCCAAGCCG AGTAGTGTCT TCAACTCGGT GCGTCTCTCT AGGAGCCGCG CGGGAAGGAT  
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 60 TTCTGAATAC AAAGTGATGT GTTAAATAC TGCAATAAA GTGATACTGA AACAC-3' (FRAG. No: ) (SEQ ID NO:11834)

# **Eotaxin Antisense Nucleic Acids and Oligonucleotide Fragments**

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 70 CCCCATTGCT ATCCCTGTG ACCTGTGGG AATGTTCCTC CTCTCTCTC TTCTCTCTG GAATCTGTG AAGGTCTGG  
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 75 GAAGAAGTGG GTGCAGGATT CCATGAAGTA TCTGGACCAA AAATCTCAA CTCCAAGCC ATAA CCACATATTC



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 GCTACAGGAG AATCACCAGT GGCAAAATGTC CCCAGAAAGC TGTGATCTTC AAGACCAAAC TGGCCAAAGGA TATCTGTGCC  
 40 GACCCCAAGA AGAAGTGGGT GCAGGATTC ATGAAGTATC TGGACCAAAA ATCTCCAAT CCAAAGCCAT AAATAATCAG  
 CATTTTTGAA ACCAAACAGG AGCCTGAGTG TTGCTTAATT TGTCTTCCCT TCTTACAATG CATTCTGAGG TAACCTCATT  
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 45 GGAATAC-3' (FRAG.NO.: ) (SEQ ID NO:11860)  
 5'-ATGAAGGTCT CCGCAGCAT TCTGTGGCTG CTGCTCATAG CAGCTGCCTT CAGCCCCCAG GGGCTCGCTG GGCCAGCTTC  
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 GTGGCAATG TCCCAGAAA GCTGTGATCT TCAAGACCAA ACTGGCCAAAG GATATCTGTG CCGACCCCAA GAAGAAGTGG  
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 50 5'-CCACATATTC CCTCTCTTT CCAAGGCAAG ATCCAGATGG ATTAATAAAT GTACCAAGTC CTCTCTACTA GCTTGCCTCT  
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# **FK-506 Binding Protein Nucleic Acids and Oligonucleotide Fragments**

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15 CCGGTGTCA TCCTCCCAA TGCCACCCTC ATCTTTGACG TGGAGCTGCT CAACCTAGAG TGAAGGCAGG AAGGAACTCA  
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35 ACTGCAATGC TGGACACTAC AGGTATCTGT CCGTGGGCCA CAGGGACCT CTGAAGCCTT CTTTGTGGCC TTTTTTTTTT  
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5'-GCCAGGTCG TGTGGTCCA CGCCGCCCGT CGCGCCGCC GCGCGCTCAG CGTCCGCCGC CGCCATGGGA-3' (FRAG.  
50 No:\_) (SEQ ID NO:11864)

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60 CACAAGGTGC TCAGACATGA AATGTACATG GCGTACCGTA CACAGAGGGA CTGAGCCAG TTACCTTTCG TGTCACTTTC  
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65 CCGGATGCTG TGAAGATGGA AAGAAATTTG ATTCTCCCGG GGACAGAAAC AAGCCCTTTA AGTTTATGCT AGGCAAGCAG  
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70 TCAGCTTTGC TTCCACACC TCTGTTCTT CTCCCTTTT CTCTCGTAT GTGTGTTTAC CTAAACTATA TGCCATAAAC  
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CAGATTTGAG GCGCTGTTGA GGAAGTGAAT ACTCTCCAAG TTGAGAGATG TCTTTGGGTT AAATTAAGG CCGTACCTAA  
75 AACTGAGGTG GGGATGGGGA GAGCCTTTC CTCCACCATT CCCACCCACC CTCCCTTAA ACCCTCTGCC TTTGAAAGTA

wherein B is adenosine, or, more preferably, replaces adenosine and is an "equivalent" or a "universal" base, and adenosine A2a receptor agonist or only minimally antagonist, an adenosine A2b receptor antagonist, an adenosine A3 receptor antagonist, or an adenosine A1 receptor antagonist. Similarly, adenosine (A) may always be replaced by an "alternative", "equivalent" and/or "universal" base having a small fraction, preferably less than 0.3 of the activity of adenosine at the adenosine receptor(s), as described above.

ggttgcgtcttgttgcgcc (SEQ ID NO:11031)  
gcccgcgcgcctg (SEQ ID NO:11051)  
gcccgtctccccggc (SEQ ID NO:11052)  
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253

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25 t g g a a c t c t c c t g t g a g a t g g c c a a g g c c t g a a c t a c c t g c c g g g g a g c a c c t t g g g g t t t g c c c a g g c a a c a g c g  
g c c t g t t c c a a g g c a t c c t g g a g c a g t g g t g g a t g g g c c c a c a c c c a c a g a c a g a c t g c g c c t g g a g a c c t g g a t g a  
g a g t g g c a g c t a c t g g g t c a g t g a c a a g a g g t g c c c c c t g c t c a c t c a g c c a g g c c c t c a c t a c t c c c g g a c a t c a  
c c a c a c c c c a a c c a g t g c t g c t c c a a a g c t g g c c a g g t g g c c a g a a g a g c c t g a g a g a c a g a g g c t g g a g g c  
c t g t g c a g c c c t c a g c t g c c a a c a g c a a g t g g a a g t t a c c a a c a g c c c a c a t t c c t g g a g g t g c t a g a g g a t t c c c g t c  
30 c c t g c g g g t g t c t g c t g g c t t c c t g c t t t c c a g c t c c c a t t c t g a a g c c a g g t t c t a c t c c a t c a g c t c c t c c c g g  
a t c a c a g c c c a c g g a g a t c c a c c t g a c t g t g g c c g t g g t c a c c t a c c a c a c g g a g a t g g c c a g g g t c c c t g c a c c a c  
g g t g t c g c a g c a c a t g g c t c a a c a g c c t g a a g t t a c c a a c a g c c c a g t g c c c t g c t t g t g c g g a a t g c c a g c g c c t t c c a  
c c t c c c c a g g a t c c c t c c a t c c t t g c a t c c t c a t c g g g c c t g g c a a g g a t c g t g c c c t t c c g c a g t t t c t g g c a g c  
a a c g g c t c c a t g a c t c c c a g c a c a a g g a g t g c g g g g a g g c c g a t g a c c t t g g t g t t g g g t g c c c g c c c c a g a t g a g  
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g c c t g g c a a g c c a a g g t c t a t g t t c a g g a c a t c c t c g g c a g c a g c t g g c c a g c a g g t g c t c c g t g t g c t c c a a a g g  
a g c a g g c c a c c t c t a t g t t g c g g g a t g t g c g c a t g g c c c g g a c g t g g c c a c a c c c t g a a g c a g c t g g t g g c t g c c  
a a g c t g a a a t g a a t g a g g a g c a g g t c g a g g a c t a t t c t t c a g c t c a a g a g c c a a g c g t a c g a a g a t a t c t t  
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c c t c t a a c a a g t a g c a c c c t g g a t t g a t c g g a g c c t c c t c t c a a a c t g g g g c c t c c t g g t c c c t t g g a g a c a a a t  
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649

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20 **Table : Exemplary Genes and oligos**

HUMAN GENES	SEQ ID NOS. Nucleic acid (amino acid)	SEQ ID NOS. of oligos (No. of Oligonucleotide Fragments)	GENEBANK ACCESSION NOS. For the Genes
H2A histone family, member N	3285	3286-3364 (79)	AI095013
tubulin, beta polypeptide	3365	3366-3405 (40)	AI672565
ELL gene (11-19 lysine-rich leukemia gene)	3406	3407-3509 (103)	AI652901
7-dehydrocholesterol reductase	3510	3511-3592 (82)	AI652764
karyopherin alpha 2 (RAG cohort 1, importin alpha 1)	3593	3594-3680 (87)	AA489087
ADP-ribosylation factor-like 7	3681	3682-3709 (28)	AA281534
EST	3710	3711-3740 (30)	AI038433
EST	3741	3742-3808 (67)	AI122689
EST	3809	3810-3862 (53)	AI092623
ESTs	3863	3864-3936 (73)	AI095492
ESTs	3937	3938-3990 (53)	AI138216
ESTs	3991	3992-4059 (68)	AI128305
ESTs	4060	4061-4123 (63)	AI125228
ESTs	4124	4125-4181 (57)	AI041482
ESTs	4182	4183-4258 (76)	AI051839
Homo sapiens mRNA; cDNA DKFZp434A1716 (from clone DKFZp434A1716)	4259	4260-4328 (69)	AI092429
ESTs	4329	4330-4362 (33)	AI096522
ESTs	4363	4364-4421 (58)	AI122807
ESTs	4422	4423-4483 (61)	AI041212
EST	4484	4485-4544 (60)	AI125651
enolase 1, (alpha)	4545	4546-4629 (84)	AI001174
EST	4630	4631-4683 (53)	AI024215
EST	4684	4685-4729 (45)	AI034360
Homo sapiens mRNA; cDNA DKFZp564H0764 (from clone DKFZp564H0764)	4730	4731-4788 (58)	AA465687
Homo sapiens mRNA for KIAA1363 protein, partial cds	4789	4790-4853 (64)	AI085559
potassium voltage-gated channel, shaker-related subfamily, beta member 2	4854	4855-4920 (66)	AI654215
ER-associated DNAJ; ER- associated Hsp40 co- chaperone; hDj9; ERj3	4921	4922-4948 (27)	AA505075
ESTs, Weakly similar to p38 protein [H.sapiens]	4949	4950-5008 (59)	AA906703
CGI-142	5009	5010-5084 (75)	AI369870

ESTs	5085	5086-5138 (53)	AA463249
Homo sapiens clone 25058 mRNA sequence	5139	5140-5165 (26)	R38894
ESTs	5166	5167-5203 (37)	R49144
squamous cell carcinoma antigen 1	5204	5205-5290 (86)	AA398883
ESTs	5291	5292-5349 (58)	AA425700
myosin X	9 (10)	1628-2922 (1295)	NM_012334, AA187977
ESTs	5350	5351-5395 (45)	AA459692
epithelial protein lost in neoplasm beta	5396	5397-5453 (57)	AA487557
CD44 antigen (homing function and Indian blood group system)	5454	5455-5509 (55)	T69168
coagulation factor III (thromboplastin, tissue factor)	5510	5511-5588 (78)	AI313387
ESTs	5589	5590-5646 (57)	AA909635
adducin 1 (alpha)	5647	5648-5705 (58)	R00103
5' nucleotidase (CD73)	5706	5707-5767 (61)	N35316
ESTs, Moderately similar to semaphorin C [M.musculus]	5768	5769-5823 (55)	AA293300
ESTs	5824	5825-5892 (68)	AA278764
ESTs	5893	5894-5926 (33)	AA678160
calmodulin 2 (phosphorylase kinase, delta)	11 (12)	2923-3107 (185)	NM_001743, AA663941
ESTs	5927	5928-5996 (69)	R42770
high-mobility group (nonhistone chromosomal) protein 17	5997	5998-6095 (98)	H93087
chloride intracellular channel 1	6096	6097-6177 (81)	AA486518
ubiquitin carrier protein	6178	6179-6208 (30)	AA464729
transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)	1 (2)	13-552 (540)	M55153, R97066
tubulin, alpha 1 (testis specific)	6209	6210-6270 (61)	AA180912
sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican)	6271	6272-6343 (72)	AA436142
proteasome (prosome, macropain) 26S subunit, non-ATPase, 2	6344	6345-6413 (69)	H05893
tubulin, beta polypeptide	6414	6415-6485 (71)	H37989
filamin B, beta (actin-binding protein-278)	6486	6487-6551 (65)	AA486238
stannocalcin	5 (6)	677-1323 (647)	NM_003155, AA085318
low density lipoprotein receptor (familial hypercholesterolemia)	6552	6553-6609 (57)	AA504461
plectin 1, intermediate filament binding protein, 500kD	6610	6611-6683 (73)	AA448400
S100 calcium-binding protein A2	3 (4)	553-676 (124)	BC002829, AA458884
Immediate early response 3	6684	6685-6735 (51)	AA480815
calpain, large polypeptide L2	6736	6737-6831 (95)	AA102454
pleckstrin homology-like domain, family A, member 1	6832	6833-6900 (68)	AA258396
melanoma adhesion molecule	6901	6902-6979 (78)	AA497002
CD44 antigen (homing function and Indian blood group system)	6980	6981-7069 (89)	AA282906
programmed cell death 5	7070	7071-7159 (89)	AA156940
hexokinase 1	7160	7161-7209 (49)	AA485272
vascular endothelial growth factor	7210	7211-7290 (80)	R19956
integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)	7291	7292-7396 (105)	AA463610
calumenin	7397	7398-7471 (74)	R78585
syntaxin 11	7472	7473-7526 (54)	R33851
diphtheria toxin receptor	7527	7528-7578 (51)	R14663

(heparin-binding epidermal growth factor-like growth factor) Fn14 for type I transmembrane protein	7579	7580-7632 (53)	R33355
Nef-associated factor 1	7633	7634-7694 (61)	T64626
high-mobility group (nonhistone chromosomal) protein isoforms I and Y	7695	7696-7753 (58)	AA448261
catechol-O-methyltransferase	7754	7755-7796 (42)	R44202
C-terminal binding protein 1	7797	7798-7864 (67)	W81570
collagen, type XVII, alpha 1	7865	7866-7932 (67)	AA128561
ESTs	7933	7934-8029 (96)	N58473
farnesyl-diphosphate farnesyltransferase 1	8030	8031-8107 (77)	AA679352
RNA helicase-related protein	8108	8109-8147 (39)	N55459
Interferon stimulated gene (20kD)	8148	8149-8230 (82)	AA150500
steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)	8231	8232-8283 (52)	H16833
prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	8284	8285-8345 (61)	AA644211
laminin, alpha 3 (nicein (150kD), kalinin (165kD), BM600 (150kD), epiligrin)	8346	8347-8440 (94)	AA001432
collagen, type XVII, alpha 1	8441	8442-8494 (53)	H87536
keratin 18	8495	8496-8601 (106)	AA664179
heparan sulfate (glucosamine) 3-O-sulfotransferase 1	8602	8603-8652 (50)	H86812
tubulin, alpha 2	8653	8654-8765 (112)	AA626698
adenylyl cyclase-associated protein	8766	8767-8833 (67)	R37953
forkhead box D1	8834	8835-8897 (63)	AA069372
cathepsin C	7 (8)	1324-1627 (304)	NM_001814, AA644088
ESTs, Highly similar to AF151802_1 CGI-44 protein [H.sapiens]	8898	8899-8985 (87)	T74688
ribonucleotide reductase M2 polypeptide	8986	8987-9056 (70)	AA187351
laminin, gamma 2 (nicein (100kD), kalinin (105kD), BM600 (100kD), Herlitz junctional epidermolysis bullosa))	9057	9058-9133 (76)	AA677534
Homo sapiens mRNA; cDNA DKFZp586P1622 (from clone DKFZp586P1622)	9134	9135-9221 (87)	T59658
ESTs, Weakly similar to /prediction	9222	9223-9289 (67)	AA284245
lactate dehydrogenase A	9290	9291-9369 (79)	H05914
Total			
98 genes		9369 (9277)	

(GENBANK ACCESSION NO. M55153)

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 (SEQ ID NO: 1)

Amino acid sequence for G-protein G-alpha H (GENBANK ACCESSION No. M55153)

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 35 ValAlaCysThrValLeuArgCysLeuGlyIleProThrArgValValThrAsnTyrAsnSerAlaHisAspGlnAsnSerAsnLeuIleLeuTyrPheArgAsnGluPheGlyGluI  
 eGlnGlyAspLysSerGluMetIleTrpAsnPheHisCysTrpValGluSerTrpMetThrArgProAspLeuGlnProGlyTyrGluGlyTrpGlnAlaLeuAspProThrProGlnGlu  
 LysSerGluGlyThrTyrCysCysGlyProValProValArgAlaIleLysGluGlyAspLeuSerThrLysTyrAspAlaProPheValPheAlaGluValAsnAlaAspValValAspTr  
 pIleGlnGlnAspAspGlySerValHisLysSerIleAsnArgSerLeuIleValGlyLeuLysIleSerThrLysSerValGlyArgAspGluArgGluAspIleThrHisThrTyrLysTyrPr  
 oGluGlySerSerGluGluArgGluAlaPheThrArgAlaAsnHisLeuAsnLysLeuAlaGluLysGluGluThrGlyMetAlaMetArgIleArgValGlyGlnSerMetAsnMetGl  
 40 ySerAspPheAspValPheAlaHisIleThrAsnAsnThrAlaGluGluTyrValCysArgLeuLeuLeuCysAlaArgThrValSerTyrAsnGlyIleLeuGlyProGluCysGlyThr  
 LysTyrLeuLeuAsnLeuThrLeuGluProPheSerGluLysSerValProLeuCysIleLeuTyrGluLysTyrArgAspCysLeuThrGluSerAsnLeuIleLysValArgAlaLeuLe  
 uValGluProValIleAsnGluAlaGluArgAspLeuTyrLeuGluAsnProGluIleLysIleArgIleLeuGlyGluProLysGlnLysArgLysLeuValAlaGluValSer  
 LeuGlnAsnProLeuProValAlaLeuGluGlyCysThrPheThrValGluGlyAlaGlyLeuThrGluGluGlnLysThrValGluIleProAspProValGluAlaGlyGluGluValLy  
 sValArgMetAspLeuValProLeuHisMetGlyLeuHisLysLeuValValAsnPheGluSerAspLysLeuLysAlaValLysGlyPheArgAsnValIleIleGlyProAla (SEQ  
 45 ID NO: 2).

(GENBANK ACCESSION NO. BC002829)

GGCAGCAGGCTCCCTCACCCCGTCCAGGATGCCAGTCCCCACGACACCTCCCACTTCCCACTGTGGCCTGGGTGGGCTCAGGG  
 TGTGCCCTTGACCTGGCCTAGAGCCCTCCCCAGCTGGTGGTGGAGCTGGCACTCTCTGGGAGGGAGGGGGCTGGGAGGGGAATGAG  
 50 GTGGAAATGGCAAGAGGCCAGGCTTTGGTGGGATCAGGTTGAGGCAAGGTTTGGTTTCTTAAATGCCAAGTTGGGGGCGAGTGGGG  
 CCCACATATAAATCCTCACCTGGGAGCCTGGCTGCCTTCTCTCTCTCTGGGTCTGTCTCTGCCACCTGGTCTGCCACAGATCCAT  
 GATGTGCAGTTCTCTGGAGCAGGCGCTGGCTGTGCTGGTCACTACCTTCCACAAGTACTCTCTGCCAAGAGGGCGCAAGTTCAAGCT  
 GAGTAAGGGGGAAATGAAGGAACCTTCTGCACAAGGAGCTGCCAGCTTTGTGGGGAGAAAGTGGATGAGGAGGGGCTGAAGAA  
 CTGATGGGCAGCCTGGATGAGAAACAGTGACCAAGGAGCTGAGGAGTATGCTGTTTCTGGCACTCATCACTGTCTATGTGTG  
 55 AATGACTTCTTCCAGGCTGCCAGACCGACCTGAAGCAGAACTCTTGACTTCTGCCATGGATCTTTTGGGCCAGGACTGTGTA  
 TGCCTTTGAGTTTGTATTCAATAAACTTTTGTGCTGTTGAAAAA

(SEQ ID NO: 3)

Amino acid sequence for S100A2 (GENBANK ACCESSION No. BC002829)

MetMetCysSerSerLeuGluGlnAlaLeuAlaValLeuValThrPheHisLysTyrSerCysGlnGluGlyAspLysPheLysLeuSerLysGlyGluMetLysGluLeuHis  
 LysGluLeuProSerPheValGlyGluLysValAspGluGluGlyLeuLysLysLeuMetGlySerLeuAspGluAsnSerAspGlnGlnValAspPheGlnGluTyrAlaValPheLe  
 60 uAlaLeuIleThrValMetCysAsnAspPhePheGlnGlyCysProAspArgPro (SEQ ID NO: 4).

(GENBANK ACCESSION NO. NM\_003155)

CAGTTTGCAAAAGCCAGAGGTGCAAGAAGCAGCGACTGCAGCAGCAGCAGCAGCAGCGGCGGTGGCAGCAGCAGCAGCAGCGGC  
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 65 ACCTAAGCTTTCACTGTATCCAGATCCACATCTTCACTAAGCCAGGAGAGGGAAGAGGAAAGGGGGCAGGAAAGAAAAA  
 CCCAACAACTTAGCGAACTTCTCAGAGAATGCTCCAAACTCAGCAGTGTCTTCTGGTGTGGTGATCAGTGCTTCTGCAACCCAT  
 GAGGCGGAGCAGAAATGACTCTGTGAGCCCCAGGAAATCCGAGTGGCGGCTCAAACTCAGCTGAAAGTGGTTGCTTGCCTCAACAG  
 TCTCTCAGGTGGCTGGCTGGCTGGCTGGAACTCCACTGTGACACAGATGGGATGTATGACATCTGTAAATCCTT  
 70 TCTGTACAGCGTGTCTAAATTTGACACTCAGGGAAAAAGCATTCGTCAAAGAGAGCTTAAATGTCATCGCAACGGGGTCACTCCA  
 AGGTCTTCTCGCCATTTCGGAGGTGCTCCACTTCCAAAGGATGATTGCTGAGGTGCAGGAAGAGTGTACAGCAAGCTGAATGTGT  
 GCAGCATCGCAAGCGGAACCTGAAGCCATCACTGAGGTGCTCCAGCTGCCAATCACTTCTCCAACAGATACTATAACAGACTT

GTCCGAAGCCTGCTGGAATGTGATGAAGACACAGTCAGCACAATCAGAGACAGCCTGATGGAGAAAAATTGGGCCTAACATGGCCA  
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AAGCTGAAAGTCTCTCCTCAGGAACCTCCGAGGTGAGGAGGACTCTCCCTCCACATCAAACGCACATCCCATGAGAGTGCATAACC  
AGGGAGAGGTTATTCACAACTCACCAAAATACTAGTATCATTTTAGGGGTGTGACACACCAATTTTGAGTGTACTGTGCTGGTTTGA  
5 TTTTAAAAAGTAGTCTCTATTTCTATCCCTTAAAGAAAAATGTGCAAGAACTAGGCTTCTGTAATCAATATCCCAACATTCGCA  
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GTCTTTTCCCTGCTCCCTGAGACCACCCCAACACAAAACATTCATGTAACCTCTCCAGCCATGTAAATTTGAAGATGTGGATCC  
CTTTAGAACGGTTGCCCCAGTAGAGTTAGCTGATAAGGAACTTTATTTAAATGCATGTCTTAAATGCTCATAAAGATGTTAAATGG  
10 AATTCGTGTTATGAATCTGTGCTGGCCATGGACGAATATGAATGTCACTTTGAATTCCTGATCTCTAATGAGCTAGTGTCTTATGGT  
CTTGATCTCTCAATGTCTAATTTCTTTCCGACACATTTACCAAAATGCTTGAGCCTGGCTGTCCAACCAGACTTTGAGCCTGCATCT  
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AACAAGCAGTATATAAATTAATTTATGTCATATAGATTTAGTTTGTAACTTAGCTTTATTTTCTTTTCTGGGAATGGAATTAAC  
15 TCTCACTTCCAGATATCCACATAAATGCTCCTTTGTGGCCTTTTATACTAAGGGGTAGAAGTAGTTTAAATCAACATCAAACT  
TAAGATGGGCCTGTATGAGACAGGAAAAACCAACAGGTTTATCTGAAGGACCCAGGTAAAGATGTTAATCTCCAGCCACCTCAA  
CCCAGAGGCTACTCTTGACTTAGACCTATACTGAAAGATCTCTGTACATCCAACCTGGAATTCAGGAACCAAAAGAGCATCCCT  
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20 GCCAAAGTAGTCTGGCAGCTGGACCATCTCTGTAGGATCGTAAAAAATGAAAAAAGAAAAAAGAAAAAGAGAGGGA  
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CAGTAGTTTCTCAGGGTCACTGTCTTGAACCCACAGTCCCTTATGAGCGTCACTGCCACCAAAAGGTCAATGTCAAGAGAGGAA  
GAGAGGGAGGAGGGGTAGGACTGACAGGGGCCACTCCAACTGCTTAGGTAGAACTATTTGGTGTCTGACTCTCACTAGGCTAAAC  
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25 ACCATAAAGCCTTTAAACCCAGTAAAGTGTCTCAAGGACCAAGAGCAATTGCAGCAGACCCAGCAGCAGCAGCAGCAGCAAA  
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30 AGCCAGGACCCCAATGCGACAAGTAGTTTCATGAGTATTCCTAGCAAAATTTCTCTTCTTCTCAGTTTCACTAGATTTCCTTTTCTTT  
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ATTCCCCCTTAACTTCCAAAGCTTCGTCTTGTGTTTGTCTGACAGATGATTTCGGGGGCTGACCTAGACCACTTTGCAATGTTCTCT  
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35 AGTACTGGAATAAACAGTGAAGCATATCTGGTATATGTCATTATTTATTTGTTAAATACATTTTAAAGCTCCATGTGCATATAAAGGT  
TATGAAACATATCATGTAATGACAGATGCAAGTTATTTATTTGCTTTATTTTATAATTAAGATGCCATAGCATAATATGAAGCC  
TTTGGTGAATTCCTTCTAAGATAAAAAATAATAAAGTGTTCCTTTATTTGTTTCAAAAAAAGAAAAAAGAAAAA  
(SEQ ID NO: 5)

Amino acid sequence for Stanniocalcin 1 (GENBANK ACCESSION No. NM\_003155)

MetLeuGlnAsnSerAlaValLeuLeuValLeuValIleSerAlaSerAlaThrHisGluAlaGluGlnAsnAspSerValSerProArgLysSerA  
rgValAlaAlaGlnAsnSerAlaValValAlaValArgCysLeuAsnSerAlaLeuGlnValGlyCysGlyAlaPheAlaCysLeuGluAsnSerThrCy  
40 sAspThrAspGlyMetTyrAspIleCysLysSerPheLeuTyrSerAlaAlaLysPheAspThrGlnGlyLysAlaPheValLysGluSerLeuLys  
CysIleAlaAsnGlyValThrSerLysValPheLeuAlaIleArgArgCysSerThrPheGlnArgMetIleAlaGluValGlnGluGluCysTyrS  
erLysLeuAsnValCysSerIleAlaLysArgAsnProGluAlaIleThrGluValValGlnLeuProAsnHisPheSerAsnArgTyrTyrAsnAr  
gLeuValArgSerLeuAspGluSerPheLeuValSerThrIleArgAspSerLeuMetGluLysIleGlyProAsnMetAlaSerLeuPhe  
45 HisIleLeuGlnThrAspHisCysAlaGlnThrHisProArgAlaAspPheAsnArgArgArgThrAsnGluProGlnLysLeuLysValLeuLeuA  
rgAsnLeuArgGlyGluGluAspSerProSerHisIleLysArgThrSerHisGluSerAla (SEQ ID NO: 6).

(GENBANK ACCESSION NO. NM\_001814)

AATTCTTACCTCTTTTCTCAGCTCCCTGCAGCATGGGTGCTGGGCCCTCCTTGCTGCTCGCCGCCCTCCTGCTGCTTCTCTCCGGCG  
ACGGCGCGCTGCGCTGCGACACACCTGCCAATGCACCTATCTTGACCTGCTGGGCACCTGGGTCTTCCAGGTGGGCTCCAGCGGTT  
50 CCCAGCGCATGTCACTGCTCGGTTATGGGACCACAAGAAAAAAGTAGTGGTGTACCTTCAGAAGCTGGATACAGCATATGAT  
CCTATTGGCAATCTGGCCATTTCACCATTCATAACCAAGGCTTGTGATTTGTTGAATGACTACAAGTGGTTGCTTTTGA  
AGTATAAAGAAGAGGGCAGCAAGGTGACCACTTACTGCAACGAGACAATGACTGGGTGGGTGCATGATGTGTTGGGCCGGAACGTG  
GGCTTGTTCACCGGAAAGAAGGTGGGAACCTGCTCTGAGAATGTGTATGTCAACACAGCACACCTTAAGAAATTCAGGAAAAAGT  
60 ATTCTAATAGGCTCTACAAGTATGATCACAACTTTGTGAAAGCTATCAATGCCATTGAGAGTCTTGGACTGCAACTACATACATGG  
AATATGAGACTCTTACCTCGGGAGATATGATTAGGAGAATGGTGGGCCACAGTCGAAAAATCCCAAGGCCCAACCTGACCACTG  
55 ACTGCTGAAATACAGCAAAAGATTTGCAATTTGCCAACATCTTGGGACTGGAGAAATGTTTCATGGTATCAATTTGTCTAGTCTGTT  
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CAGAACCCCAATCCTAAGCCCTCAGGAGGTTGTCTTGTAGCCAGTATGCTCAAGGCTGTGAAGCGGCTTCCCATACCTTATGCA  
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65 ATAGCAGTGGCAGCCACACCAATTCCTAAATTTGATAGGATATGCTTCCAGTATTTTCAATATGATCTGCATCAGTTGTAAGGGGAAT  
TGGTATATTTACAGACTGTAGACTTTCAGCAGCAATCTCAGAAGCTTACAAATAGATTTCCATGAAGATATTTGTCTTCAGAATTAA  
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GTCAGCTATGAAGTAATAGAGTTTGTCTTAATCATTTGTAATTCAAACATGCTATATTTTTTAAATCAATGTGAAAAATAGACTTAT  
70 TTTTAAATGTACCAATCACAAGAAAAATAATGGCAATAATTATCAAACTTTTAAATAGATGCTCATATTTTAAAAATAAGTTTT  
AAAAATACTGC  
(SEQ ID NO: 7)

Amino acid sequence for Cathepsin C

(GENBANK ACCESSION No. NM\_001814)

MetGlyAlaGlyProSerLeuLeuLeuAlaAlaLeuLeuLeuLeuSerGlyAspGlyAlaValArgCysAspThrProAlaAsnCysThrTyrL

euAspLeuLeuGlyThrTrpValPheGlnValGlySerSerGlySerGlnArgAspValAsnCysSerValMetGlyProGlnGluLysLysValVal  
1ValTyrLeuGlnLysLeuAspThrAlaTyrAspAspLeuGlyAsnSerGlyHisPheThrIleIleTyrAsnGlnGlyPheGluIleValLeuAsn  
AspTyrLysTrpPheAlaPhePheLysTyrLysGluGluGlySerLysValThrThrTyrCysAsnGluThrMetThrGlyTrpValHisAspValL  
euGlyArgAsnTrpAlaCysPheThrGlyLysLysValGlyThrAlaSerGluAsnValTyrValAsnThrAlaHisLeuLysAsnSerGlnGluLy  
5sTyrSerAsnArgLeuTyrLysTyrAspHisAsnPheValLysAlaIleAsnAlaIleGlnLysSerTrpThrAlaThrThrTyrMetGluTyrGlu  
ThrLeuThrLeuGlyAspMetIleArgArgSerGlyGlyHisSerArgLysIleProArgProLysProAlaProLeuThrAlaGlnGlnLys  
ysIleLeuHisLeuProThrSerTrpAspTrpArgAsnValHisGlyIleAsnPheValSerProValArgAsnGlnAlaSerCysGlySerCysTy  
rSerPheAlaSerMetGlyMetLeuGluAlaArgIleArgIleLeuThrAsnAsnSerGlnThrProIleLeuSerProGlnGluValValSerCys  
10SerGlnTyrAlaGlnGlyCysGluGlyGlyPheProTyrLeuIleAlaGlyLysTyrAlaGlnAspPheGlyLeuValGluGluAlaCysPheProT  
yrThrGlyThrAspSerProCysLysMetLysGluAspCysPheArgTyrTyrSerSerGluTyrHisTyrValGlyGlyPheTyrGlyGlyCysAs  
nGluLeuMetLysLeuGluLeuValHisHisGlyProMetAlaValAlaPheGluValTyrAspAspPheLeuHisTyrLysLysGlyIleTyr  
HisHisThrGlyLeuArgAspProPheAsnProPheGluLeuThrAsnHisAlaValLeuLeuValGlyTyrGlyThrAspSerAlaSerGlyMetA  
spTyrTrpIleValLysAsnSerTrpGlyThrGlyTrpGlyGluAsnGlyTyrPheArgIleArgArgGlyThrAspGluCysAlaIleGluSerIl  
eAlaValAlaAlaThrProIleProLysLeu (SEQ ID NO: 8).

(GENBANK ACCESSION NO. NM\_012334)

GAGACAAAGGCTGCCGTCCGGACGGGCGAGTGTAGGGACTTGGGTTTGGGCGAACAAAAAGGTGAGAAGGACAAGAAGGGACCGGG  
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20GTATTCACTTACAAGCAGAGCAAAATTACCCACAGAAAGGTGACTGCTATGCACCCACGAACGAGGAGGGCGTGGATGACATGGC  
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TACAACAACAACCTCTAGTCGCTTTGGGAAGTTTGTTCAGCTGAACATCTGTGCAGAAAGGAAATATTCAGGCGGGGAGAATTGTAGA  
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CAGCCAGTGGCAGCAGCAGGTGCTGCTGCCCATCAGTGCAAGGACTCCGGGAGCCTACACAACCTCTCCAGCGCGAGTCCCA  
CCTACTGCATGCCCGAAGCGTGGGGACTTGGCTCCCCAGACGGCGACTACGACTACGACCAGGATGACTATGAGGACGGTGCC  
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70GATGATGAGCTTTCATACCGGCTGACTCTGTGTACAGCTGTGCTTCCCGTATTTCCACAGCTTCTGTACATGAAAGGTTGGCC  
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CAGCGTGTGAGTCAGGTCCACGCTCCACGGACCAGGAGATCCAGGAGATGCATGATGAGCAGGCAAAACCCACAGAAATGCTGTG  
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65CGGTGCTGCTGCAACGCGACACGGAGGAGATGCTACCAACCTGATTAACCTGCTGCAGAGGTCCAAAGGGGACACGAGAG  
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uSerArgArgAsnTrpLysLysArgTrpPheValLeuArgGlnSerLysLeuMetTyrPheGluAsnAspSerGluGluLysLeuLysGlyThrVal  
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 erProGluAspAlaSerGlnTrpPheSerValLeuSerGlnValHisAlaSerThrAspGlnGluIleGlnGluMetHisAspGluGlnAlaAsnPr  
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 5 AsnArgValLeuHisCysAsnAlaAspThrProGluGluMetHisHisTrpIleThrLeuLeuGlnArgSerLysGlyAspThrArgValGluGlyG  
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(GENBANK ACCESSION NO. NM\_001743)

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 (SEQ ID NO: 11)

55 Amino acid sequence for Calmodulin 2 (GENBANK ACCESSION No. NM\_001743)

MetAlaAspGlnLeuThrGluGluGlnIleAlaGluPheLysGluAlaPheSerLeuPheAspLysAspGlyAspGlyThrIleThrThrLysGluL  
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 60 AsnGlyTyrIleSerAlaAlaGluLeuArgHisValMetThrAsnLeuGlyGluLysLeuThrAspGluGluValAspGluMetIleArgGluAlaA  
 spIleAspGlyAspGlyGlnValAsnTyrGluGluPheValGlnMetMetThrAlaLys (SEQ ID NO: 12).

SEQ ID NO, GENBANK ACCESSION NO., Length of oligo, Position of First nucleotide of oligo in target nucleic acid, Sequence of oligo

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65 3849, AI092623,,20,80,AGGCCCGCCCCCGCCTC,,  
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3852, AI092623,,20,62,TCAGCTTCTGTCTGAAGAAA,,  
3853, AI092623,,20,56,TCTGTCTGAAGAAATGGCCT,,  
70 3854, AI092623,,20,50,GAAGAAATGGCCTCCTGGG,,  
3855, AI092623,,20,44,AATGGCCTCCTGGGGCCGAT,,  
3856, AI092623,,20,38,CTCCTGGGGCCGATTGGTC,,  
3857, AI092623,,20,32,GGGCCGATTTGGTCTTTTCA,,  
3858, AI092623,,20,26,ATTGGTCTTTTCAAAAAA,,  
75 3859, AI092623,,20,20,TCTTTTCAAAAAA,,

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(SEQ ID NO: 3863)  
  
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3873, AI095492,,20,383,AGACGAAAGCCAGAAAGACTC,,  
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25 3876, AI095492,,20,365,TCAGCAAGCTAGCTTACCTA,,  
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711

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10 3997,AII28305,,20,374,GTACCAAGCTAACAAAATAC,,  
3998,AII28305,,20,368,AGCTAACAAAATACTCCTTG,,  
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20 4007,AII28305,,20,314,GAGAAGATTTGACTTCCACC,,  
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25 4012,AII28305,,20,284,ATTAAGCAAGTGAGCATTCC,,  
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65 4052,AII28305,,20,44,CTCAATAAAATGGTCATTGA,,  
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70 4057,AII28305,,20,14,AAAAAAAAAAAAAAAA,,  
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75 CAGCCATACTTCACTTCCACTCTGATGTTTCCAGTCATAATTACTGCTTAAATATTCTTTTATACCATGCTAGATTTTCCAATTGGT



ATGGCAGCCTATTGCTGAAAGCCACCTTAAACACTTTTAACTCAACATCCTTTTTTACAAAGGAGCAAATTGATGTTATGATTTTCAT  
CTAATACTATAACAATAAAAAAGGAAATAAGTCCCAAATGAATATTTAAATAACCAAAAAATTGTTATGTAATTTAAATCAGGAAG  
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(SEQ ID NO: 4060)

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4064,AII25228,,20,356,TCCTACTATCTAACTTACCA,,

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4065,AII25228,,20,350,TATCTAACTTACCAAACTTC,,  
4066,AII25228,,20,344,ACTTACCAAACTTCTGATT,,  
4067,AII25228,,20,338,CAAACCTCCTGATTTTAATT,,  
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4069,AII25228,,20,326,TTTAAATTACATAACAATT,,

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4070,AII25228,,20,320,TTACATAACAATTTTTTGGT,,  
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4077,AII25228,,20,278,TTATTTCTTTTTTTATTGTT,,  
4078,AII25228,,20,272,CCTTTTTTATTGTTATAGTA,,  
4079,AII25228,,20,266,TTATGTTTATAGTATTAGAT,,

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4089,AII25228,,20,206,TTGAGTTAAAAAGTGTTTTAA,,

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4090,AII25228,,20,200,TAAAAAGTGTTTTAAAGGTGGC,,  
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4092,AII25228,,20,188,AAGGTGGCTTTTCAGCAATAG,,  
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4109,AII25228,,20,86,AATGAAGTATGGCTGAGAAA,,

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4116,AII25228,,20,44,TGGAGTTCATTCCAATAAAA,,  
4117,AII25228,,20,38,TCATTCCAATAAAATGAAAT,,  
4118,AII25228,,20,32,CAATAAAATGAAATTATAGA,,  
4119,AII25228,,20,26,AATGAAATTATAGAACTTA,,

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4120,AII25228,,20,20,ATTATAGAAACTTAAAAAAA,,  
4121,AII25228,,20,14,GAAACTTAAAAAAAAAAAAA,,  
4122,AII25228,,20,8,TAAAAAAAAAAAAAAAAAAAAA,,  
4123,AII25228,,20,2,AAAAAAAAAAAAAAAAAAAAA,,  
(GENBANK ACCESSION NO. AI041482)

70

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GTACAGTAGATTATACAGTACATAATAATGAATAGTAATAAGTGACCACATTACTGGTTATATATTTTATACTATTTATTGTTA  
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(SEQ ID NO: 4124)

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5 4128, AI041482,,20,324,TCTTCTGAAGCATCTGCTTG,,  
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10 4133, AI041482,,20,294,TTGAGTTAACTTTTCTTTT,,  
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15 4138, AI041482,,20,264,AAGGAATACATTCTAAAATA,,  
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4141, AI041482,,20,246,TAACAATAAATAGTATAAAA,,  
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4177, AI041482,,20,30,AAATGTTATGAGAGCACTGT,,  
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4180, AI041482,,20,12,GTCAAAAAA,,  
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(GENBANK ACCESSION NO. AI051839)  
60 TTTTTTTTTTTTTTTTTTTTTTTTTTTTAAAGTAACTAAGTTTCTGTTTTAATGATATATTTAGGAAATCTGATATCATTTCAGTAT  
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CATCCCGCTTCCATCTCAAGGCTCTGGGCACCCCTCTTGCAGACTGCTTCTATTTCTTTGGACAGTTTGGGAAAAATCACGCTCTT  
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65 TCTAATGCGCACAGCATCCACAGTGAGCAGCCACC  
(SEQ ID NO: 4182)  
  
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4184, AI051839,,20,448,TGCTCACTGTGGGATGCTGT,,  
70 4185, AI051839,,20,442,CTGTGGGATGCTGTGCGATT,,  
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4187, AI051839,,20,430,GTGCGATTAGACAGTTACTA,,  
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75 4936, AA505075,,20,75,TTTCATTCAAAATGCCAACT,,

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10 4946,AA505075,,20,15,AAAAA,,  
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75 5004,AA906703,,20,26,TATTACTGAAAGACACATTT,,

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5 5076, A1369870,,20,52, TGGTCGCGCGAAGATGCCG,,  
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(GENBANK ACCESSION NO. R38894)

TTTTTTACAGCATAGCGGTTTATTCATGCCATCATACAGTCGATCTGTATTCTTCAAGTACATTTTGAATTATAATGAAGACAGTTT  
AAGGCATAACTCTTCCCCTCAAATCTATGGTCTTTCTCAAGTGAGACACTAGAGAGAGTAGAANGGGAGGNTGAGATAGGGC  
(SEQ ID NO: 5139)

5 5140,R38894,,20,152,GCCCTATCTCANCCTCCCNT,,  
5141,R38894,,20,146,TCTCANCCTCCNTTCTACT,,  
5142,R38894,,20,140,CCTCCNTTCTACTCTCTCT,,  
5143,R38894,,20,134,NTTCTACTCTCTCTAGTGTC,,  
5144,R38894,,20,128,CTCTCTCTAGTGCTCACTT,,  
10 5145,R38894,,20,122,CTAGTGCTCACTTGAGAAA,,  
5146,R38894,,20,116,TCTCACTTGAGAAAGACCAT,,  
5147,R38894,,20,110,TTGAGAAAGACCATAGATT,,  
5148,R38894,,20,104,AAGACCATAGATTGAGTGG,,  
5149,R38894,,20,98,ATAGATTGAGTGGGAAGAG,,  
15 5150,R38894,,20,92,TTGAGTGGGAAGAGTTATGC,,  
5151,R38894,,20,86,GGGAAGAGTTATGCCTTAAA,,  
5152,R38894,,20,80,AGTTATGCCTTAACTGTCT,,  
5153,R38894,,20,74,GCCTTAACTGTCTTCATTA,,  
5154,R38894,,20,68,AACTGTCTTCATTATAAAATT,,  
20 5155,R38894,,20,62,CTTCATTATAAAATTCAAAAT,,  
5156,R38894,,20,56,TATAAATTCAAAATGTACTT,,  
5157,R38894,,20,50,TTCAAAATGTACTTGAAGAA,,  
5158,R38894,,20,44,ATGTACTTGAAGAAATACAGA,,  
5159,R38894,,20,38,TTGAAGAAATACAGATCGACT,,  
25 5160,R38894,,20,32,AATACAGATCGACTGTATGA,,  
5161,R38894,,20,26,GATCGACTGTATGATGGCAT,,  
5162,R38894,,20,20,CTGTATGATGGCATGAATAA,,  
5163,R38894,,20,14,GATGGCATGAATAAACCGCT,,  
5164,R38894,,20,8,ATGAATAAACCGCTATGCTG,,  
30 5165,R38894,,20,2,AAACCGCTATGCTGTAAAAA,,  
(GENBANK ACCESSION NO. R49144)  
TTTTTTTTTTTTTTGGAGATGACCTGNACTTTTAAATGGCACAGCCCCAGCTCCAGCAAAGCAGCAAGACAGGAAGCTATGCAAAGC  
TGCTCAGAGGTGCAGTGGCCAAACAACCTAGGAGATCGCCTGTNTCCCTCCCATCCCCCAAGCTTATGACGTGGCTCCATGCCCA  
GGGAACCTTTGGGCCANCCCANCCCCANTCCCAAACCTCATAATNCACAGAGGGAGCCTGGGCCAAG  
35 (SEQ ID NO: 5166)

5167,R49144,,20,222,CTTGGCCCAGGCTCCCTCTG,,  
5168,R49144,,20,216,CCAGGCTCCCTCTGTGNATT,,  
5169,R49144,,20,210,TCCCTCTGTGNATTATGAGG,,  
40 5170,R49144,,20,204,TGTGNATTATGAGGGTTTGG,,  
5171,R49144,,20,198,TTATGAGGGTTTGGGANTGG,,  
5172,R49144,,20,192,GGGTTTGGGANTGGGGNTGG,,  
5173,R49144,,20,186,GGGANTGGGGNTGGGNTGGC,,  
5174,R49144,,20,180,GGGGNTGGGNTGGCCCAAAG,,  
45 5175,R49144,,20,174,GGGNTGGCCCAAAGTCCCT,,  
5176,R49144,,20,168,GCCCAAAGTTCCTGGGCAT,,  
5177,R49144,,20,162,AGTTCCTGGGCATGGAGCC,,  
5178,R49144,,20,156,CTGGGCATGGAGCCACGTCA,,  
5179,R49144,,20,150,ATGGAGCCACGTCAATAGCT,,  
50 5180,R49144,,20,144,CCACGTCATAAGCTTGGGGG,,  
5181,R49144,,20,138,CATAAGCTTGGGGATGGGA,,  
5182,R49144,,20,132,CTTGGGGATGGGAGGGAAN,,  
5183,R49144,,20,126,GGATGGGAGGGAANACAGGC,,  
5184,R49144,,20,120,GAGGGAANACAGGCGATCTC,,  
55 5185,R49144,,20,114,ANACAGGCGATCTCCTAGAG,,  
5186,R49144,,20,108,GCGATCTCCTAGAGTTGTT,,  
5187,R49144,,20,102,TCCTAGAGTTGTTTGCCAC,,  
5188,R49144,,20,96,AGTTGTTTGCCACTGCACC,,  
5189,R49144,,20,90,TTGGCCACTGCACCTCTGAG,,  
60 5190,R49144,,20,84,ACTGCACCTCTGAGCAGCTT,,  
5191,R49144,,20,78,CCTCTGAGCAGCTTTGCATA,,  
5192,R49144,,20,72,AGCAGCTTTGCATAGCTTCC,,  
5193,R49144,,20,66,TTTGCATAGCTTCTGTCTT,,  
5194,R49144,,20,60,TAGCTTCTGTCTTGCTGCT,,  
65 5195,R49144,,20,54,CCTGTCTTGCTGCTTTGCTG,,  
5196,R49144,,20,48,TTGCTGCTTTGCTGGAGCTG,,  
5197,R49144,,20,42,CTTGCTGGAGCTGGGGCTG,,  
5198,R49144,,20,36,TGGAGCTGGGGCTGTGCCAT,,  
5199,R49144,,20,30,TGGGGCTGTGCCATTAAG,,  
70 5200,R49144,,20,24,TGTGCCATTAAGTNCAGG,,  
5201,R49144,,20,18,ATTAAGTNCAGGTCATCT,,  
5202,R49144,,20,12,AGTNCAGGTCATCCAAAA,,  
5203,R49144,,20,6,GGTCATCTCAAAAAA,,  
(GENBANK ACCESSION NO. AA398883)

TATGTCACTATTTTATTGATGATGTGTTTTATAGAATCACAAATTTAGAAACATAAGAAGGATTTAGGTATCACCTAAATTCAAAG  
AAATGTGTGTTTCTAGGTTGCTAAATTCAAAGAAAAAGTATGATTTGGTTGGTTTCATTAAAAACAGGTCACAAACAGAATTATATT  
TCAATTTAGAAAGATACGGTATTAAGTGATTCATCTTATTTTGGACATTTTCTCAAGGAGAAATTTTCTGGAAGAAAAAGTACATT  
TATATGTGGGCTTATTAAGAGAAAGAGAGAAAGGCATGCTATTTAATCATTAATTTCTTGATGATGACGATCATCATCAAGATGAG  
5 AAAGAAAAAGAAATATGAGCCAAGAGAATCTGTTGTTGCCAGCAATCAGTTTACCAGAACATCTGCAGGTGAACATTTTCCAAATGG  
AGTGACAGACTAATTGCATCTACGGGGATGAGAATCTGCCATAGAGAGGATGCTGTGGGCTTATTTTGCTTATGTAGATAGGAAGG  
GTGATACATGGA  
(SEQ ID NO: 5204)

10 5205,AA398883,,20,514,TCCATGTATCACCCCTTCCTA,,  
5206,AA398883,,20,508,TATCACCCCTTCCTATCTACA,,  
5207,AA398883,,20,502,CCTTCCTATCTACATAAGCA,,  
5208,AA398883,,20,496,TATCTACATAAGCAAAATAA,,  
5209,AA398883,,20,490,CATAAGCAAAATAAGCCAC,,  
15 5210,AA398883,,20,484,CAAAATAAGCCACAGCATC,,  
5211,AA398883,,20,478,AAGCCACAGCATCCTCTCT,,  
5212,AA398883,,20,472,ACAGCATCCTCTCTATGGCA,,  
5213,AA398883,,20,466,TCCTCTCTATGGCAGATTCT,,  
5214,AA398883,,20,460,CTATGGCAGATTCTCATCCC,,  
20 5215,AA398883,,20,454,CAGATTCTCATCCCCGTAGA,,  
5216,AA398883,,20,448,CTCATCCCCGTAGATGCAAT,,  
5217,AA398883,,20,442,CCCGTAGATGCAATTAGTCT,,  
5218,AA398883,,20,436,GATGCAATTAGTCTGTCACT,,  
5219,AA398883,,20,430,ATTAGTCTGTCACTCCATTT,,  
25 5220,AA398883,,20,424,CTGTCACTCCATTTGGAAAA,,  
5221,AA398883,,20,418,CTCCATTTGGAAAAATGTTCA,,  
5222,AA398883,,20,412,TTGGAAAAATGTTACCTGCA,,  
5223,AA398883,,20,406,AATGTTACCTGCAGATGTT,,  
5224,AA398883,,20,400,CACCTGCAGATGTTCTGGTA,,  
30 5225,AA398883,,20,394,CAGATGTTCTGGTAAACTGA,,  
5226,AA398883,,20,388,TTCTGGTAAACTGATTGCTG,,  
5227,AA398883,,20,382,TAAACTGATTGCTGGCAACA,,  
5228,AA398883,,20,376,GATTGCTGGCAACAACAGAT,,  
5229,AA398883,,20,370,TGGCAACAACAGATTCTCTT,,  
35 5230,AA398883,,20,364,CAACAGATTCTCTTGGCTCA,,  
5231,AA398883,,20,358,ATTCTCTTGGCTCATATTTCT,,  
5232,AA398883,,20,352,TTGGCTCATATTTCTTTCT,,  
5233,AA398883,,20,346,CATATTTCTTTCTTTCTCA,,  
5234,AA398883,,20,340,TCTTTTCTTTCTCATCTTGA,,  
40 5235,AA398883,,20,334,CTTTCTCATCTTGATGATGA,,  
5236,AA398883,,20,328,CATCTTGATGATGATCGTCA,,  
5237,AA398883,,20,322,GATGATGATCGTCATCATCA,,  
5238,AA398883,,20,316,GATCGTCATCATCAAGAATT,,  
5239,AA398883,,20,310,CATCATCAAGAATTTAATGA,,  
45 5240,AA398883,,20,304,CAAGAAATTTAATGATTAATA,,  
5241,AA398883,,20,298,TTTAATGATTAATAATAGCAT,,  
5242,AA398883,,20,292,GATTAATAATAGCATGCCTTT,,  
5243,AA398883,,20,286,AATAGCATGCCTTTCTCTCT,,  
5244,AA398883,,20,280,ATGCCTTTCTCTCTTTCTCT,,  
50 5245,AA398883,,20,274,TTCTCTCTTTCTCTTAATAA,,  
5246,AA398883,,20,268,CTTTCTCTTAATAAGCCAC,,  
5247,AA398883,,20,262,CTTAATAAGCCACATATAA,,  
5248,AA398883,,20,256,AAGCCACATATAAATGTAC,,  
5249,AA398883,,20,250,ACATATAAATGTACTTTTCT,,  
55 5250,AA398883,,20,244,AAATGTACTTTTCTTCCAG,,  
5251,AA398883,,20,238,ACTTTTCTTCCAGAAAAAT,,  
5252,AA398883,,20,232,TCTTCCAGAAAAATCTCCT,,  
5253,AA398883,,20,226,AGAAAAATCTCCTTGAGGA,,  
5254,AA398883,,20,220,ATTCTCCTTGAGGAAAAATG,,  
60 5255,AA398883,,20,214,CTTGAGGAAAAATGTCCAAA,,  
5256,AA398883,,20,208,GAAAAATGTCCAAAATAAGA,,  
5257,AA398883,,20,202,TGTCCAAAATAAGATGAATC,,  
5258,AA398883,,20,196,AAATAAGATGAATCACTTAA,,  
5259,AA398883,,20,190,GATGAATCACTTAATACCGT,,  
65 5260,AA398883,,20,184,TCACCTTAATACCGTATCTTC,,  
5261,AA398883,,20,178,AATACCGTATCTTCTAAATT,,  
5262,AA398883,,20,172,GTATCTTCTAAATTTGAAAT,,  
5263,AA398883,,20,166,TCTAAATTTGAAATATAATT,,  
5264,AA398883,,20,160,TTTGAAATATAATTCTGTTT,,  
70 5265,AA398883,,20,154,ATATAATTCTGTTTGTGACC,,  
5266,AA398883,,20,148,TTCTGTTTGTGACCTGTTTT,,  
5267,AA398883,,20,142,TTGTGACCTGTTTTAAATGA,,  
5268,AA398883,,20,136,CCTGTTTTAAATGAACCAAA,,  
5269,AA398883,,20,130,TTAAATGAACCAAAACCAAT,,  
75 5270,AA398883,,20,124,GAACCAAAACCAATCATACT,,



5271,AA398883,,20,118,AACCAAATCATACTTTTCT,,  
5272,AA398883,,20,112,ATCATACTTTTCTTTGAAT,,  
5273,AA398883,,20,106,CTTTTCTTTGAATTTAGCA,,  
5274,AA398883,,20,100,CTTTGAATTTAGCAACCTAG,,  
5 5275,AA398883,,20,94,ATTTAGCAACCTAGAAACAC,,  
5276,AA398883,,20,88,CAACCTAGAAACACACATTT,,  
5277,AA398883,,20,82,AGAAACACACATTTCTTTGA,,  
5278,AA398883,,20,76,ACACATTTCTTTGAATTTAG,,  
5279,AA398883,,20,70,TTCTTTGAATTTAGGTGATA,,  
10 5280,AA398883,,20,64,GAATTTAGGTGATACCTAAA,,  
5281,AA398883,,20,58,AGGTGATACCTAAATCCTTC,,  
5282,AA398883,,20,52,TACCTAAATCCTTCTTATGT,,  
5283,AA398883,,20,46,AATCCTTCTTATGTTTCTAA,,  
5284,AA398883,,20,40,TCTTATGTTTCTAAATTTTG,,  
15 5285,AA398883,,20,34,GTTCCTAAATTTTGTGATTC,,  
5286,AA398883,,20,28,AAATTTTGTGATTCTATAAAA,,  
5287,AA398883,,20,22,TGTGATTCTATAAAACACAT,,  
5288,AA398883,,20,16,TCTATAAAACACATCATCAA,,  
5289,AA398883,,20,10,AAACACATCATCAATAAAAT,,  
20 5290,AA398883,,20,4,ATCATCAATAAAATAGTGAC,,  
(GENBANK ACCESSION NO. AA425700)  
CACATTTTATTAAATCTTTTATTGGAATCAAGGGAACCCCTCATATGGAGAATAGAGACCCAAAGAACAGTTGGGATCAAGAGCTTAT  
TTACTTTTAAAGAAATGATACATTTGTGGAAATTTGATCAATAAAGAGCTTTAGGCTAAGGGCAGTAAATTGTGGCATGACTAAG  
AAATAGATGGTGGATATGAGTGGAAAGATAAGGAGTATTTTCAGTAGATTTGTTTGTACAGATCCATTTCTGCATCTACTCCAGTCTC  
25 CAGTAAGGATGTTCTTCTTCTCTGGAACAGAAAGGGGCACITTTCTCATGGGAAATTTGATTACCTGCTTTTAGGGAGACAGCAGGTCA  
GGGAACCCCTTCCTG  
(SEQ ID NO: 5291)

5292,AA425700,,20,343,CAGGAAGGGTTCCTGACCT,,  
30 5293,AA425700,,20,337,GGGTTCCTGACCTGCTGTC,,  
5294,AA425700,,20,331,CCTGACCTGCTGCTCCCTA,,  
5295,AA425700,,20,325,CTGCTGTCTCCCTAAAAGCA,,  
5296,AA425700,,20,319,TCTCCCTAAAAGCAGGTAAT,,  
5297,AA425700,,20,313,TAAAAGCAGGTAATACAATT,,  
35 5298,AA425700,,20,307,CAGGTAATACAAATTTCCCAT,,  
5299,AA425700,,20,301,ATACAATTTCCCATGAGAAA,,  
5300,AA425700,,20,295,TTTCCCATGAGAAAGTGCCC,,  
5301,AA425700,,20,289,ATGAGAAAGTGCCCTTCTG,,  
5302,AA425700,,20,283,AAGTGCCCTTCTGTCCAG,,  
40 5303,AA425700,,20,277,CCCTTCTGTTCCAGAAGAGA,,  
5304,AA425700,,20,271,TGTTCAGAAGAGAAGAACA,,  
5305,AA425700,,20,265,AGAAGAGAAGAACATCCTTA,,  
5306,AA425700,,20,259,GAAGAACATCCTTACTGGAG,,  
5307,AA425700,,20,253,CATCCTTACTGGAGACTGGG,,  
45 5308,AA425700,,20,247,TACTGGAGACTGGGAGTAGA,,  
5309,AA425700,,20,241,AGACTGGGAGTAGATGACGA,,  
5310,AA425700,,20,235,GGAGTAGATGACGAAATGGA,,  
5311,AA425700,,20,229,GATGACGAAATGGATCTGTA,,  
5312,AA425700,,20,223,GAAATGGATCTGTACAAACA,,  
50 5313,AA425700,,20,217,GATCTGTACAAACAAATCTA,,  
5314,AA425700,,20,211,TACAAACAAATCTACTGAAA,,  
5315,AA425700,,20,205,CAAATCTACTGAAATACTCC,,  
5316,AA425700,,20,199,TACTGAAATACTCCTTATCT,,  
5317,AA425700,,20,193,AATACTCCTTATCTTCCACT,,  
55 5318,AA425700,,20,187,CCTTATCTTCCACTCATATC,,  
5319,AA425700,,20,181,CTTCCACTCATATCCACCAT,,  
5320,AA425700,,20,175,CTCATATCCACCATCTATTT,,  
5321,AA425700,,20,169,TCCACCATCTATTTCTTAGT,,  
5322,AA425700,,20,163,ATCTATTTCTTAGTCATGCC,,  
60 5323,AA425700,,20,157,TTCTTAGTCATGCCACAATT,,  
5324,AA425700,,20,151,GTCTAGGCCACAATTTACTGC,,  
5325,AA425700,,20,145,CCACAATTTACTGCCCTTAG,,  
5326,AA425700,,20,139,TTTACTGCCCTTAGCCTAAA,,  
5327,AA425700,,20,133,GCCCTTAGCCTAAAGCTCTT,,  
65 5328,AA425700,,20,127,AGCCTAAAGCTCTTATTTG,,  
5329,AA425700,,20,121,AAGCTCTTTATTTGATCAAT,,  
5330,AA425700,,20,115,TTTATTTGATCAATTTTCCA,,  
5331,AA425700,,20,109,TGATCAATTTTCCACAAATG,,  
5332,AA425700,,20,103,ATTTTCCACAAATGTATCAT,,  
70 5333,AA425700,,20,97,CACAAATGTATCATTCTTT,,  
5334,AA425700,,20,91,TGTATCATTTCTTTAAAAAG,,  
5335,AA425700,,20,85,ATTTCTTTAAAAAGTAAATA,,  
5336,AA425700,,20,79,TTAAAAAGTAAATAAGCTCT,,  
5337,AA425700,,20,73,AGTAAATAAGCTCTTGATCC,,  
75 5338,AA425700,,20,67,TAAGCTCTTGATCCCAACTG,,

5339,AA425700,,20,61,CTTGATCCCAACTGTTCTTT,,  
5340,AA425700,,20,55,CCCAACTGTTCTTTGGGTCT,,  
5341,AA425700,,20,49,TGTTCTTTGGGTCTCTATTC,,  
5342,AA425700,,20,43,TTGGGTCTCTATTTCCATA,,  
5 5343,AA425700,,20,37,CTCTATTCTCCATATGAGGG,,  
5344,AA425700,,20,31,TCTCCATATGAGGGTTCCCT,,  
5345,AA425700,,20,25,TATGAGGGTTCCCTTGATT,,  
5346,AA425700,,20,19,GGTTCCCTTGATTCAAATAA,,  
5347,AA425700,,20,13,CTTGATTCAAATAAAAGATT,,  
10 5348,AA425700,,20,7,TCAAATAAAAGATTAAATAA,,  
5349,AA425700,,20,1,AAAAGATTAAATAAAATGTG,,  
(GENBANK ACCESSION NO. AA459692)  
GCCTGTTAATACAGTAGTTGTAATAATGTACGTGATTAGCAAGGAAACATAAACCTGCCTGGAATAAACTGTAAACCATGGAATAT  
CAGACACCTGCCTGATATTCTCACTACAAACATTTTCGTGGTCAAAATTGTCTCTGACGATGATGGTCATTTGGAGAACAAAAACAG  
15 CAAAGCAAGAGGAGAGAACAAGAGTATCCTGAGGCGGTCTCTGCACTGCTCATAGCTGTTCTCTTACCTTCCACCTGGTGGCC  
CTGACTAGACCTCCAGAGAATTCC  
(SEQ ID NO: 5350)

5351,AA459692,,20,267,GGAATTCTCTGGAGGTCTAG,,  
20 5352,AA459692,,20,261,CTCTGGAGGTCTAGTCCAGG,,  
5353,AA459692,,20,255,AGGTCTAGTCCAGGGCCACC,,  
5354,AA459692,,20,249,AGTCCAGGGCCACCAGGTGG,,  
5355,AA459692,,20,243,GGGCCACCAGGTGGAAGGCT,,  
5356,AA459692,,20,237,CCAGGTGGAAGGCTAAGGAG,,  
25 5357,AA459692,,20,231,GGAAGGCTAAGGAGGAACAG,,  
5358,AA459692,,20,225,CTAAGGAGGAACAGCTATGA,,  
5359,AA459692,,20,219,AGGAACAGCTATGAGCACTG,,  
5360,AA459692,,20,213,AGCTATGAGCACTGCAGGAG,,  
5361,AA459692,,20,207,GAGCACTGCAGGAGACCGCC,,  
30 5362,AA459692,,20,201,TGCAGGAGACCGCCTCAGGA,,  
5363,AA459692,,20,195,AGACCGCCTCAGGATACTCT,,  
5364,AA459692,,20,189,CCTCAGGATACTCTTGTCT,,  
5365,AA459692,,20,183,GATACTCTTGTCTCTCCTC,,  
5366,AA459692,,20,177,CTTGTCTCTCTCTCTGCTT,,  
35 5367,AA459692,,20,171,CTCTCTCTCTGCTTTGCTGT,,  
5368,AA459692,,20,165,TCTTGCTTTGCTGTTTTGT,,  
5369,AA459692,,20,159,TTTGCTGTTTTGTCTCCA,,  
5370,AA459692,,20,153,GTTTTTGTCTCCAAATGAC,,  
5371,AA459692,,20,147,GTCTCCAAATGACCATCAT,,  
40 5372,AA459692,,20,141,CAAATGACCATCATCGTCAG,,  
5373,AA459692,,20,135,ACCATCATCGTCAGAAGACA,,  
5374,AA459692,,20,129,ATCGTCAGAAGACAAATTTG,,  
5375,AA459692,,20,123,AGAAGACAATTTGACCACG,,  
5376,AA459692,,20,117,CAATTTTGACCACGAAATGT,,  
45 5377,AA459692,,20,111,TGACCACGAAATGTTGTAG,,  
5378,AA459692,,20,105,CGAAATGTTGTAGTGAGAA,,  
5379,AA459692,,20,99,GTGTGTAGTGAGAAATATCAG,,  
5380,AA459692,,20,93,AGTGAGAATATCAGGCAGGT,,  
5381,AA459692,,20,87,AATATCAGGCAGGTGTCTGA,,  
50 5382,AA459692,,20,81,AGGCAGGTGTCTGATATTCC,,  
5383,AA459692,,20,75,GTGTCTGATATTCCATGGTT,,  
5384,AA459692,,20,69,GATATTCCATGGTTTACAGT,,  
5385,AA459692,,20,63,CCATGGTTTACAGTTTATTC,,  
5386,AA459692,,20,57,TTTACAGTTTATCCAGGCA,,  
55 5387,AA459692,,20,51,GTATTATCCAGGCAGGTTTA,,  
5388,AA459692,,20,45,TCCAGGCAGGTTTATGTTTC,,  
5389,AA459692,,20,39,CAGGTTTATGTTTCCTTGCT,,  
5390,AA459692,,20,33,TATGTTTCCTTGCTAATACA,,  
5391,AA459692,,20,27,TCCTTGCTAATACCGTACA,,  
60 5392,AA459692,,20,21,CTAATACACGTACAATTTTA,,  
5393,AA459692,,20,15,CACGTACAATTTTACAACATA,,  
5394,AA459692,,20,9,CAATTTTACAACACTGTAT,,  
5395,AA459692,,20,3,TACAACACTGTATTAAACAG,,  
(GENBANK ACCESSION NO. AA487557)  
65 TTTTCAAATTTTAATTAATAAATCTTTATTGAATAAAATGTTTCAGACTAGGTAAGACTAAGAAAGCAGAATGTTTACATCTCTAAA  
AAATATTAAGCTAAATCTCTATAAAATGCAGTACAAAGAAAAGCCTACAGCTTAAGACACCTCTCCCTCCCATCCATACAATTTGGA  
ATATCAACTGTGTACAAACAAATGTACTCAAGTTTATAATGTCCCCAACCTTAAGACTAGAAAAATCATCCCAAGAAAAAGGCCTAT  
AGTTGGTTTAATTTACCCCTGAGAATACTGTGATAAAAAATCAATATATTTACAGAGCTAGTAAGTATTTAAAAAATTAGTGTCTCAAAA  
AGGGGACATC  
70 (SEQ ID NO: 5396)

5397,AA487557,,20,338,GATGTCCCCTTTTTGAGACA,,  
5398,AA487557,,20,332,CCCTTTTTGAGACACTAATT,,  
5399,AA487557,,20,326,TTGAGACACTAATTTTTAAA,,  
75 5400,AA487557,,20,320,CACTAATTTTTAAATACTTA,,

5401,AA487557,,20,314,TTTTTAAATACTTACTAGCT,,  
5402,AA487557,,20,308,AATACTTACTAGCTCTGAAA,,  
5403,AA487557,,20,302,TACTAGCTCTGAAATATATT,,  
5404,AA487557,,20,296,CTCTGAAATATATTGATTTT,,  
5 5405,AA487557,,20,290,AATATATTGATTTTATCAC,,  
5406,AA487557,,20,284,TIGATTTTATCACAGTATT,,  
5407,AA487557,,20,278,TTATCACAGTATTCTCAGG,,  
5408,AA487557,,20,272,ACAGTATTCTCAGGGTGAAG,,  
5409,AA487557,,20,266,TTCTCAGGGTGAATTAAC,,  
10 5410,AA487557,,20,260,GGGTGAATTAACCAACTA,,  
5411,AA487557,,20,254,AATTAACCAACTATAGGCC,,  
5412,AA487557,,20,248,ACCAACTATAGGCCTTTTTC,,  
5413,AA487557,,20,242,TATAGGCCTTTTCTTGGA,,  
5414,AA487557,,20,236,CCTTTTCTTGGGATGATTT,,  
15 5415,AA487557,,20,230,TCTTGGGATGATTTCTAGT,,  
5416,AA487557,,20,224,GATGATTTCTAGCTTAAG,,  
5417,AA487557,,20,218,TTTCTAGCTTAAGGTTTGG,,  
5418,AA487557,,20,212,GTCTTAAGGTTTGGGGACAT,,  
5419,AA487557,,20,206,AGGTTTGGGGACATTATAAA,,  
20 5420,AA487557,,20,200,GGGGACATTATAAACTTGAG,,  
5421,AA487557,,20,194,ATTATAAACTTGAGTACATT,,  
5422,AA487557,,20,188,AACTTGAGTACATTGTGTGT,,  
5423,AA487557,,20,182,AGTACATTGTGTACACAG,,  
5424,AA487557,,20,176,TTGTGTACACAGTTGATA,,  
25 5425,AA487557,,20,170,GTACACAGTTGATATTCCAA,,  
5426,AA487557,,20,164,AGTTGATATTCCAAATTGTA,,  
5427,AA487557,,20,158,TATTCCAAATTGTATGGATG,,  
5428,AA487557,,20,152,AAATTGTATGGATGGGAGGG,,  
5429,AA487557,,20,146,TATGGATGGGAGGGAGAGGT,,  
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5449,AA487557,,20,26,CTGAAACATTTTATTCAT,,  
50 5450,AA487557,,20,20,CATTTTATTCATAAAGAT,,  
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55 CAATAANGTGCNTTTCAACTCAGCAATATACATATCANTGCTNTTCTCTATTANTTAATTGATCCATCAATAAATATACAAAAACCA  
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35 5504,T69168,,20,32,ATGAGGAAANGCANTGATAT,,  
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45 AGGAAGGTGCCCAGAATACCAATGTCTCCTGCACCTTAACACATTAATACAAAGTTGCCAATTGTTTTGAATTTCCAAATGTATTCC  
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60 5521,AI313387,,20,404,AGGAAATTTGGGTGCATTTCT,,  
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55 AAAATGCAATCAAACTTACATATCTTTAAATATTCGAAAGTCAGATTTTGTCTGATTGCCCTATCCAATTAGGGCAAATTAGTGA  
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60 5590, AA909635,,20,339,ATATGAAGTTAGTATACAGC,,  
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75 5604, AA909635,,20,255,CATATGTTTATGACAGTTTC,,

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25 5629,AA909635,,20,105,GAATATTTAAAGATATGTA,,  
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40 5644,AA909635,,20,15,GGAAACCTGTTTTAATAAAT,,  
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45 GGGGCTGGCCTCAGTAGGGGCTCAGTGGGGCTTGGGGTCTATGGGCTTCTCTCTCTAACATTGGGAAGCCGAGTGCTTC  
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5711,N35316,,20,337,ATGTTTGTCTTAGTGT,,  
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5717,N35316,,20,301,CTTGATACGAAAATATACT,,  
5718,N35316,,20,295,ACGAAAATATACTTTAAAC,,  
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55 5720,N35316,,20,283,TTTAAACTTCATAACCTTT,,  
5721,N35316,,20,277,ACTTCATAACCTTTTATAA,,  
5722,N35316,,20,271,TAACCTTTTATAAAAGTTG,,  
5723,N35316,,20,265,TTTTATAAAAGTTGTCAG,,  
5724,N35316,,20,259,AAAAGTTGTTGCAGCAAAAT,,  
60 5725,N35316,,20,253,TGTTGCAGCAAAATAATAGC,,  
5726,N35316,,20,247,AGCAAAATAATAGCCTCGGT,,  
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5729,N35316,,20,229,GTCTATGCATATATGGATT,,  
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5732,N35316,,20,211,TAGCTATAAAAAATGTCAA,,  
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70 5735,N35316,,20,193,AATAAGATTGTACAAGGAAA,,  
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5738,N35316,,20,175,AAATTAGAGAAAGGCACATT,,  
5739,N35316,,20,169,GAGAAAGGCACATTTAGGGT,,  
75 5740,N35316,,20,163,GGCACATTTAGGGTTATTT,,

5741,N35316,,20,157,TTTAGGGTTTATTTTTTACA,,  
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5 5745,N35316,,20,133,GCCAGTAAATAGGGTAAAT,,  
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20 5760,N35316,,20,43,GAAATGACTTTGAACCACTT,,  
5761,N35316,,20,37,ACTTTGAACCACTTTGCAAT,,  
5762,N35316,,20,31,AACCACTTTGCAATTGTAGA,,  
5763,N35316,,20,25,TTTGCAATTGTAGATTCCCA,,  
5764,N35316,,20,19,ATTGTAGATTCCCAACAATA,,  
25 5765,N35316,,20,13,GATTCCCAACAATAAAATTG,,  
5766,N35316,,20,7,CAACAATAAAATTGAAGATA,,  
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30 TGTGCTGGGCAGTGTGTGATATCCCTTAGAGTGGAGGAAGGTGAGGGATGGAGGGTGAAGTGGGGACTGGGGAGAGGACCAGGGTG  
CAGTTAGTTCCTCGTGTGTGAGTTCAAAGATGGAGCGAGGGTGGATATGGTGGGAAGGGGCACACGGGTTCTCACGCAACAACGGA  
GGAAGGCAGCGCAGTCTCTCCCTGAATTTCTGAGGGAAAGGCGTACATTGTGCAGAAATCTCTCCTGAGCTCGCGCTGTCTCTC  
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35 5769,AA293300,,20,326,GAGAGGACAGCGCGAGCTCA,,  
5770,AA293300,,20,320,ACAGCGCGAGCTCAGGAGAG,,  
5771,AA293300,,20,314,CGAGCTCAGGAGAGATTTTCG,,  
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5773,AA293300,,20,302,AGATTTTCGTGACAATGTACG,,  
40 5774,AA293300,,20,296,CGTGACAATGTACGCCTTTC,,  
5775,AA293300,,20,290,AATGTACGCCTTTCCCTCAG,,  
5776,AA293300,,20,284,CGCCTTTCCCTCAGAATTCA,,  
5777,AA293300,,20,278,TCCCTCAGAATTCAGGGAAG,,  
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5787,AA293300,,20,218,GTGTGCCCTTCCCACCATA,,  
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60 5794,AA293300,,20,176,ACTCAAACACGAGGAACATA,,  
5795,AA293300,,20,170,ACACGAGGAACATACTGCAC,,  
5796,AA293300,,20,164,GGAACATACTGCACCCTGGT,,  
5797,AA293300,,20,158,AACTGCACCCTGGTCTCTC,,  
5798,AA293300,,20,152,ACCCTGGTCTCTCCCCAGT,,  
65 5799,AA293300,,20,146,GTCTCTCTCCCCAGTCCCCAG,,  
5800,AA293300,,20,140,TCCCCAGTCCCCAGTTCAAC,,  
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70 5804,AA293300,,20,116,ATCCCTCACCTTCTCTCCACT,,  
5805,AA293300,,20,110,CACCTTCTCTCCACTCTAAGG,,  
5806,AA293300,,20,104,CCTCCACTCTAAGGGATATC,,  
5807,AA293300,,20,98,CTCTAAGGGATATCAACACT,,  
5808,AA293300,,20,92,GGGATATCAACACTGCCAG,,  
75 5809,AA293300,,20,86,TCAACACTGCCAGCACAGG,,

5810,AA293300,,20,80,CTGCCCAGCACAGGGGCCCT,,  
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5 5814,AA293300,,20,56,TTATGTGGTTTTTATACATT,,  
5815,AA293300,,20,50,GGTTTTTATACATTTTTTAA,,  
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5818,AA293300,,20,32,AATAAGATGCACTTTATGTC,,  
10 5819,AA293300,,20,26,ATGCACTTTATGTCATTTTT,,  
5820,AA293300,,20,20,TTTATGTCATTTTTTAATAA,,  
5821,AA293300,,20,14,TCATTTTTTAATAAAGTCTG,,  
5822,AA293300,,20,8,TTTAATAAAGTCTGAAGAAT,,  
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ATACCTCGGGGAAGTGGGACTTTGTCTGACAAAGCCAGGACAAATCCCCCTACCCCAACCCAGCAGTGATTAAAAACCCGTACG  
GTCACTTTCTATGTGATGGCTGTCTCCCTCTCACCAGACTGCATAGCGGTTGCAGATGAACATTTGGCACCTAGATGGGGGTCAAGG  
20 AGCTGGGGCTGTGATTCAAGGAAGATGCTGAGGGGGACTGGGAGTCTCTGTTGAATCTTGAAGCAAGGGGTGA  
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5826,AA278764,,20,398,CTTGCTTCAAGATTCAAACA,,  
25 5827,AA278764,,20,392,TCAAGATTCAAACAGAGACT,,  
5828,AA278764,,20,386,TTCAAACAGAGACTCCCACT,,  
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5830,AA278764,,20,374,CTCCCACTCCCTCTCAGCAT,,  
5831,AA278764,,20,368,GTCCCTCTCAGCATCTTCCC,,  
30 5832,AA278764,,20,362,CTCAGCATCTTCCCTGAATC,,  
5833,AA278764,,20,356,ATCTTCCCTGAATCAACAGCC,,  
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35 5837,AA278764,,20,332,CTCCTTGACCCCATCTAGG,,  
5838,AA278764,,20,326,GACCCCATCTAGGTGCCAA,,  
5839,AA278764,,20,320,CATCTAGGTGCCAAATGTT,,  
5840,AA278764,,20,314,GGTGCCAAATGTTTCTCTGC,,  
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55 5857,AA278764,,20,212,TGGGGGTAGGGGGATTGTCC,,  
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60 5862,AA278764,,20,182,GACAAAGTCCCACTTCCCG,,  
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65 5867,AA278764,,20,152,GCCCTTGGTATCAAGTGAGG,,  
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70 5872,AA278764,,20,122,CATCACAGGGTCTCGCCCTA,,  
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5876,AA278764,,20,98,CCTGGAATTATTTCACTTTT,,  
75 5877,AA278764,,20,92,ATTATTTCACTTTTAAGATA,,

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5879,AA278764,,20,80,TTAAGATAAATGCACTATTT,,  
5880,AA278764,,20,74,TAAATGCACTATTTCACTGT,,  
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5 5882,AA278764,,20,62,TTCACTGTTTCGCCTCCCAT,,  
5883,AA278764,,20,56,GTTCGCCTCCCATTTCTAAGG,,  
5884,AA278764,,20,50,CTCCCATTTCTAAGGAGGTGA,,  
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5886,AA278764,,20,38,GGAGGTGAGGTGGTTGGAAT,,  
10 5887,AA278764,,20,32,GAGGTGGTTGGAATAAAAC,,  
5888,AA278764,,20,26,GTGGAATAAAACAGTTCC,,  
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5891,AA278764,,20,8,CCTGTCAAAAAA,,  
15 5892,AA278764,,20,2,AAAAA,,  
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ACAATCCAAGTCCGCTTCCAAATAAAGTAAAGTATTAGTATGAAAAACCCTGGCTACAATAAATTAGAGACCATTTAATCTCG  
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25 5897,AA678160,,20,177,AATATGAACCTTGACCAAGAT,,  
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5899,AA678160,,20,165,ACCAAGATTGCAGGATTA,,  
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30 5902,AA678160,,20,147,AATGGTCTCTAATTTATTGT,,  
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5909,AA678160,,20,105,ACTTTTTACTTTATTGGA,,  
5910,AA678160,,20,99,TACTTTATTGGAAGCGGAC,,  
5911,AA678160,,20,93,ATTTGGAAGCGGACTTGGAT,,  
40 5912,AA678160,,20,87,AAGCGGACTTGGATTGTACT,,  
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5921,AA678160,,20,33,AATAGAGAAAAAGACTGTGG,,  
50 5922,AA678160,,20,27,GAAAAAGACTGTGGCCCCAT,,  
5923,AA678160,,20,21,GACTGTGGCCCCATTAAAAA,,  
5924,AA678160,,20,15,GGCCCCATTAAAAAATGCT,,  
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5926,AA678160,,20,3,AAAATGCTAAATTAAGATTG,,  
55 (GENBANK ACCESSION NO. R42770)  
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60 CCCCNCACACTGTGGGATGTTTGTAGCGGGTAATTNTTGTATGGGGGGCTGTCCCTACANCGGGTTTTAGGGGGG  
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5928,R42770,,20,411,CCCCCTAAAACCCCGNTGT,,  
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65 5930,R42770,,20,399,CCCGNTGTAGGGACAGCCCC,,  
5931,R42770,,20,393,GTAGGGACAGCCCCCATA,,  
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5933,R42770,,20,381,CCCCATAACAAANAATTAC,,  
5934,R42770,,20,375,TAACAAANAATTACCCCGCT,,  
70 5935,R42770,,20,369,ANAATTACCCCGCTCAAAAC,,  
5936,R42770,,20,363,ACCCCGCTCAAAACATCCCA,,  
5937,R42770,,20,357,CTCAAAACATCCCAAGTGN,,  
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5939,R42770,,20,345,CACAGTGNCGGGGCCTGAGA,,  
75 5940,R42770,,20,339,GNCGGGGCTGAGAAACCNC,,

5941,R42770,,20,333,GCCTGAGAAACNCGGATTT,,  
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 5 5945,R42770,,20,309,AAGTCACCCNTGAGTCAAGC,,  
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 15 5955,R42770,,20,249,TCCTTATTCATTAGATTAC,,  
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 5958,R42770,,20,231,ACAGNTTTCCCTTGACTAG,,  
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 20 5960,R42770,,20,219,TTGACTAGGGGTTTGAAGNA,,  
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 5962,R42770,,20,207,TTGAAGNACTTACCGAAAT,,  
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 25 5965,R42770,,20,189,ATGCAGATATGTTAAATTTA,,  
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 5967,R42770,,20,177,TAAATTTATGATGATGGTTT,,  
 5968,R42770,,20,171,TATGATGATGGTTTGAAGAA,,  
 5969,R42770,,20,165,GATGGTTTGAAGAAACACGT,,  
 30 5970,R42770,,20,159,TTGAAGAAACACGTCTGAAG,,  
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 35 5975,R42770,,20,129,AAATAACTGGTCCAAAATAC,,  
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 5979,R42770,,20,105,TTAAATTTAATCTGCAAAAT,,  
 40 5980,R42770,,20,99,TTAATCTGCAAAATGTATAC,,  
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 5988,R42770,,20,51,TGTTTTAGTCTTCACATCA,,  
 5989,R42770,,20,45,TAGTCTTCACATCAAAATTG,,  
 50 5990,R42770,,20,39,TCACATCAAAATTGCTCTAT,,  
 5991,R42770,,20,33,CAAAATGCTCTATTAATGA,,  
 5992,R42770,,20,27,TGCTCTATTAATGAACAAAT,,  
 5993,R42770,,20,21,ATTAATGAACAAATAAAGA,,  
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 5999,H93087,,20,582,CTGAACCTAAAAACNTCCA,,  
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65 6071,H93087,,20,150,TAACCCTGCAGAAAAATGGAG,,  
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70 6076,H93087,,20,120,AGACCAGGCACAGAAAGCTG,,  
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75 6081,H93087,,20,90,AGATGCCAAGTGAAGTGTGT,,



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5 6086,H93087,,20,60,TAAGTGTGTACTTCTGGTGA,,  
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6088,H93087,,20,48,TCTGGTGAAGTGTACAGTTTG,,  
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6092,H93087,,20,24,ACTATTTTATCAAGTTT,,  
6093,H93087,,20,18,TTTATCAAGTTTATAAAA,,  
6094,H93087,,20,12,CAAGTTTATAAAAAATGCAG,,  
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CCCGGGAAGAATTCGCTTCCACCTGTCCAGATGATGAGGAGATCGAGCTCGCCTATGAGCAAGTGGCAAAGGCCCTCAAATAAGCC  
CCTCCTGGGACTCCCTCAACCCCTCCATTTTCTCCACAAAGGCCCTGGTGGTTTCCACATTGCTACCCAATGGACACACTCCAAAA  
20 TGGCCAGTGGGACAGGAATCCTGGAGCACTTGTCCGGGATGGTGTGGTGGAGAGGGGATGAGGGAAGAAATGGGGGGCCTGG  
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25 6098,AA486518,,20,475,TATTTCTGTATTTTATTACTG,,  
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35 6108,AA486518,,20,415,TGACCCAGGCCCCCCATTTC,,  
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6134,AA486518,,20,259,GTGAGGGAGTCCCAGGAGG,,  
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6146,AA486518,,20,187,TCATCTGGACAGGTGGAAGC,,  
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75 6148,AA486518,,20,175,GTGGAAGCGAATTTCTCCCG,,

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25 6173,AA486518,,20,25,TCGTTGCCATCCAGAACTT,,  
6174,AA486518,,20,19,CCATCCAGAACTTCTCTG,,  
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30 (GENBANK ACCESSION NO. AA464729)  
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(SEQ ID NO: 6178)

35 6179,AA464729,,20,180,AACTTAGAGACAGAGTTGGA,,  
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40 6183,AA464729,,20,156,GGGGACAGGAGAGGTTGGGG,,  
6184,AA464729,,20,150,AGGAGAGGTTGGGGTCACGG,,  
6185,AA464729,,20,144,GGTTGGGGTCACGGTGAAG,,  
6186,AA464729,,20,138,GGTCACGGTGAAGGAGGAA,,  
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50 6193,AA464729,,20,96,GCGCCCGCTTCTTGCCGTC,,  
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55 6198,AA464729,,20,66,CCGCCAGCTTCTTATCGCGC,,  
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6200,AA464729,,20,54,TATCGCGCTCGCCAGCATGC,,  
6201,AA464729,,20,48,GCTCGCCAGCATGCTTCTTG,,  
6202,AA464729,,20,42,CAGCATGCTTCTTGGCCATG,,  
60 6203,AA464729,,20,36,GCTTCTTGGCCATGGGACCT,,  
6204,AA464729,,20,30,TGGCCATGGGACCTGGATTT,,  
6205,AA464729,,20,24,TGGGACCTGGATTTGTTTTT,,  
6206,AA464729,,20,18,CTGGATTTGTTTTCTAAAT,,  
6207,AA464729,,20,12,TTGTTTTCTAAATAAAGTT,,  
65 6208,AA464729,,20,6,TTCTAAATAAAGTTGAAAA,,  
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70 CCCCCTGGCCACCTATGCACCAAGTCATCTGCAAGAAAGGCATACCACGAGCAGCTGTGGTGGCAGAGATCAACCAATGCCTGCT  
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(SEQ ID NO: 6209)

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6211,AA180912,,20,360,ATCACACTTTACCNCTGCTG,,

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5 6216,AA180912,,20,330,AAAAGCAGGCATTGGTGATC,,  
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6218,AA180912,,20,318,TGGTGATCTCTGCCACCGAC,,  
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6245,AA180912,,20,156,TGATGGAGGAGACAATTTGG,,  
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45 6256,AA180912,,20,90,GGTTGCGGCGGCAGATGTCA,,  
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6260,AA180912,,20,66,TTGCTTCGTTGTCCACCATG,,  
50 6261,AA180912,,20,60,CGTTGTCCACCATGAAGGCA,,  
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6265,AA180912,,20,36,CTGAGTGCTCCAGGGTGGTG,,  
55 6266,AA180912,,20,30,GCTCCAGGGTGGTGTGGTG,,  
6267,AA180912,,20,24,GGGTGGTGTGGGTGGTCAGG,,  
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6269,AA180912,,20,12,TGGTCAGGATAGAGTTGTAG,,  
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65 CAGTGGCATCCTGGGATGAGCCGGGGACAGACCTGGACAGACACGTTGTCATTGCTGCTGTGGGTAGGAAAAATGGGCGTAAAGG  
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6275,AA436142,,20,410,TACGCCCATTTTCTACCCA,,  
6276,AA436142,,20,404,CATTTTCTACCCACAGCAG,,  
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6300,AA436142,,20,260,TGGTTTTGGTCTTTTTATAA,,  
6301,AA436142,,20,254,TGGTCTTTTTATAACTTTTT,,  
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25 6303,AA436142,,20,242,AACTTTTTCTCAAAGTCACT,,  
6304,AA436142,,20,236,TTCTCAAAGTCACTGATGTT,,  
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35 6313,AA436142,,20,182,CCCATCAAATCCTGAGTGT,,  
6314,AA436142,,20,176,AAATCCTGAGTGTGAGTTTG,,  
6315,AA436142,,20,170,TGAGTGTGAGTTTGTGTTC,,  
6316,AA436142,,20,164,TCAGTTTGTGTGCTTATTG,,  
6317,AA436142,,20,158,TGTTGTCCCTATTGTAGATG,,  
40 6318,AA436142,,20,152,CCCTATTGTAGATGAAATAG,,  
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6327,AA436142,,20,98,TTTCCACGTAGACTTATCTG,,  
50 6328,AA436142,,20,92,CGTAGACTTATCTGGAATGT,,  
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6330,AA436142,,20,80,TGGAATGTGAACACAACCTCT,,  
6331,AA436142,,20,74,GTGAACACAACCTCTTGGTT,,  
6332,AA436142,,20,68,ACAACCTCTTGGTTAATAGT,,  
55 6333,AA436142,,20,62,CTTGGTTAATAGTAAATGC,,  
6334,AA436142,,20,56,TTAATAGTAAATGCTTAACT,,  
6335,AA436142,,20,50,GTAAATGCTTAACTGTAGTC,,  
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6337,AA436142,,20,38,CTGTAGTCCTGAGTAGGTGC,,  
60 6338,AA436142,,20,32,TCCTGAGTAGGTGCATTCT,,  
6339,AA436142,,20,26,GTAGGTGCATTCTGTCTGT,,  
6340,AA436142,,20,20,GCATTCTGTCTGTCTCAAT,,  
6341,AA436142,,20,14,CTGTCTGTCTCAATAAATTT,,  
6342,AA436142,,20,8,GTCTCAATAAATTTTACTTT,,  
65 6343,AA436142,,20,2,ATAAATTTTACTTTGTCTGC,,  
(GENBANK ACCESSION NO. H05893)  
TTTTTTTTTTNACCTTGGGGATAAAAGTCTTTATTGAACAACCTTATCTCACTCAGTAACAAAAGAGCAGGAGGCGACAATCCCCC  
AGAAGTCTGCAGCCGTGTCCACCCTTGGCAGCAGGATGCATGTCTGCTGATAACATCAGCTGCAGTTCAGAGCCCCTGGTGGTCA  
TTAGAGATCAATAATTGGGGTCTTCCGAAGATTAAACAAAACCTTCCGAGAATGGGGGTAAACAGGAAGAAACTCCTCAGTGGCCAA  
70 CTGCCCGTTCCCGTGGGCCAACAACTGGGGTTGTATGCGTCTGGAACCTGTGATAGTCTTCGGNTTGCCAGCCTGGGCCCCACC  
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(SEQ ID NO: 6344)  
6345,H05893,,20,414,ACCCCGAAATGCCTGGTTT,,  
75 6346,H05893,,20,408,GAAATGCCTGGTTTACGTTT,,

6347,H05893,,20,402,CCTGGTTTACGTTTGATGAG,,  
6348,H05893,,20,396,TTACGTTTGATGAGGAAACT,,  
6349,H05893,,20,390,TTGATGAGGAAACTGCGGCC,,  
6350,H05893,,20,384,AGGAAACTGCGGCCCATTC,,  
5 6351,H05893,,20,378,CTGCGGCCCATTCGCCAGTG,,  
6352,H05893,,20,372,CCCATTCGCCAGTGCTGTC,,  
6353,H05893,,20,366,GCCAGTGCTGTCCGTGTG,,  
6354,H05893,,20,360,TGCTGTCCGTGTGGGCCA,,  
6355,H05893,,20,354,TCCGTGTGGGCCAGGCAGT,,  
10 6356,H05893,,20,348,TGGGCCAGGCAGTGATGT,,  
6357,H05893,,20,342,CAGGCAGTGATGTGGTGGG,,  
6358,H05893,,20,336,GTGGATGTGGTGGGCCAGG,,  
6359,H05893,,20,330,GTGGTGGGCCAGGCTGGCA,,  
6360,H05893,,20,324,GGCCAGGCTGGCAANCCGA,,  
15 6361,H05893,,20,318,GGCTGGCAANCCGAAGACTA,,  
6362,H05893,,20,312,CAANCCGAAGACTATCACAG,,  
6363,H05893,,20,306,GAAGACTATCACAGGGTTCC,,  
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6365,H05893,,20,294,AGGGTTCCAGACGCATACAA,,  
20 6366,H05893,,20,288,CCAGACGCATACAAACCCAG,,  
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6368,H05893,,20,276,AACCCAGTGTGTGGGCC,,  
6369,H05893,,20,270,AGTGTGTGTGGGCCACGGGG,,  
6370,H05893,,20,264,GTGGGCCACGGGGAACGGG,,  
25 6371,H05893,,20,258,CCACGGGGAACGGGCAGAAT,,  
6372,H05893,,20,252,GGAACGGGCAGAATTGCCA,,  
6373,H05893,,20,246,GGCAGAATTGGCCACTGAGG,,  
6374,H05893,,20,240,ATTGCCACTGAGGAGTTTC,,  
6375,H05893,,20,234,CACTGAGGAGTTTCTCCTG,,  
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6377,H05893,,20,222,TCTTCCTGTTACCCCATTC,,  
6378,H05893,,20,216,TGTTACCCCATTTCTGGAAG,,  
6379,H05893,,20,210,CCCCATTCTGGAAGGTTTTG,,  
6380,H05893,,20,204,CTTGGAAGGTTTTGTTAATC,,  
35 6381,H05893,,20,198,AGGTTTTGTTAATCTTCGGA,,  
6382,H05893,,20,192,TGTTAATCTTCGGAAGAACC,,  
6383,H05893,,20,186,TCTTCGGAAGAACCCCAATT,,  
6384,H05893,,20,180,GAAGAACCCCAATTATGATC,,  
6385,H05893,,20,174,CCCCAATTATGATCTCTAAG,,  
40 6386,H05893,,20,168,TTATGATCTCTAAGTGACCA,,  
6387,H05893,,20,162,TCTCTAAGTGACCACCAGGG,,  
6388,H05893,,20,156,AGTGACCACCAGGGGCTCTG,,  
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45 6391,H05893,,20,138,TGAACTGCAGCTGATGTTAT,,  
6392,H05893,,20,132,GCACTGATGTTATCAGCAG,,  
6393,H05893,,20,126,GATGTTATCAGCAGGACATG,,  
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6395,H05893,,20,114,AGGACATGCATCCTGCTGCC,,  
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6397,H05893,,20,102,CTGCTGCCAAGGGTGGACAC,,  
6398,H05893,,20,96,CCAAGGGTGGACACGGCTGC,,  
6399,H05893,,20,90,GTGGACACGGCTGCAGACTT,,  
6400,H05893,,20,84,ACGGCTGCAGACTTCTGGGG,,  
55 6401,H05893,,20,78,GCAGACTTCTGGGGGAATTG,,  
6402,H05893,,20,72,TTCTGGGGGAATTGTCGCCT,,  
6403,H05893,,20,66,GGGAATTGTGCGCTCCTGCT,,  
6404,H05893,,20,60,TGTCGCCTCCTGCTCTTTG,,  
6405,H05893,,20,54,CTCCTGCTCTTTGTTACTG,,  
60 6406,H05893,,20,48,CTCTTTTGTACTGAGTGAG,,  
6407,H05893,,20,42,TGTTACTGAGTGAGATAAGG,,  
6408,H05893,,20,36,TGAGTGAGATAAGGTTGTT,,  
6409,H05893,,20,30,AGATAAGGTTGTTCAATAAA,,  
6410,H05893,,20,24,GGTTGTTCAATAAAGACTTT,,  
65 6411,H05893,,20,18,TCAATAAAGACTTTTATCCC,,  
6412,H05893,,20,12,AAGACTTTTATCCCAAGGT,,  
6413,H05893,,20,6,TTTATCCCAAGGTNAAAAA,,  
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70 AGAATTTGTGTTTGCTGCTCTATCTGTTTTTTGTTTTTCTCTGGGGGGGTCTAGAACAGTGCTGGCACATAGTAGGCGCTCA  
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75 (SEQ ID NO: 6414)

6415,H37989,,20,425,CTTCCTTATATAGTGNCTTC,,  
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6417,H37989,,20,413,GTGNCTTCTACCCACTACNC,,  
5 6418,H37989,,20,407,TCTACCCACTACNCTTCTAC,,  
6419,H37989,,20,401,CACTACNCTTCTACCATTTT,,  
6420,H37989,,20,395,NCTTCTACCATTTTCTACTT,,  
6421,H37989,,20,389,ACCATTTTCTACTTTGGGCT,,  
6422,H37989,,20,383,TTCTACTTTGGGCTTAGGAT,,  
10 6423,H37989,,20,377,TTGGGCTTAGGATGATGGC,,  
6424,H37989,,20,371,CTTAGGATGATGGCCATTAT,,  
6425,H37989,,20,365,ATGATGGCCATTATCTACAT,,  
6426,H37989,,20,359,GCCATTATCTACATGTGTTT,,  
6427,H37989,,20,353,ATCTACATGTGTTTTCAGCA,,  
15 6428,H37989,,20,347,ATGTGTTTTCAGCACCTGGT,,  
6429,H37989,,20,341,TTTCAGCACCTGGTTGGTTC,,  
6430,H37989,,20,335,CACCTGGTTGGTTCTAAATG,,  
6431,H37989,,20,329,GTTGGTTCTAAATGGGATCT,,  
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6434,H37989,,20,311,CTGGAGACCCAGCTTCTTGG,,  
6435,H37989,,20,305,ACCCAGCTTCTTGGAGATT,,  
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6437,H37989,,20,293,GGAGATTTTAAAGAGGAAGT,,  
25 6438,H37989,,20,287,TTTTAAGAGGAAGTATTAAC,,  
6439,H37989,,20,281,GAGGAAGTATTAAGTGGACA,,  
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6441,H37989,,20,269,ACTGGACAAATGGAATGGGC,,  
6442,H37989,,20,263,CAAAATGGAATGGGCACCAAGA,,  
30 6443,H37989,,20,257,GAATGGGCACCAAGAAAGAAA,,  
6444,H37989,,20,251,GCACCAGAAAGAAATACAGG,,  
6445,H37989,,20,245,GAAAGAAATACAGGGTCACC,,  
6446,H37989,,20,239,AATACAGGGTCACCCAGAAT,,  
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35 6448,H37989,,20,227,CCCAGAATGGCAGAAACCTA,,  
6449,H37989,,20,221,ATGGCAGAAACCTAGGTTTC,,  
6450,H37989,,20,215,GAAACCTAGGTTTCCCAGAG,,  
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6452,H37989,,20,203,TCCCAGAGTGGAAAGAGAGA,,  
40 6453,H37989,,20,197,AGTGGAAAGAGAGAGGAGAC,,  
6454,H37989,,20,191,AAGAGAGAGGAGACATTCAA,,  
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6456,H37989,,20,179,ACATTCAACAAACAAGTATT,,  
6457,H37989,,20,173,AACAAACAAGTATTTATTGA,,  
45 6458,H37989,,20,167,CAAGTATTTATTGAGCGCCT,,  
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6464,H37989,,20,131,TGTTCTAGACCCCCCAGAGA,,  
6465,H37989,,20,125,AGACCCCCCAGAGAAAAA,,  
6466,H37989,,20,119,CCCCCAGAGAAAAAACAAA,,  
6467,H37989,,20,113,GAAGAAAAAACAAAAACAA,,  
55 6468,H37989,,20,107,AAAAACAAAAACAGATAGA,,  
6469,H37989,,20,101,AAAAACAAGATAGAGGCAGC,,  
6470,H37989,,20,95,AAGATAGAGGCAGCAACAC,,  
6471,H37989,,20,89,GAGGCAGCAACACAAATTC,,  
6472,H37989,,20,83,GCAAACACAAATTCTGAGGG,,  
60 6473,H37989,,20,77,ACAAATTCTGAGGGAGAGGA,,  
6474,H37989,,20,71,TCTGAGGGAGAGGAAAGGGG,,  
6475,H37989,,20,65,GGAGAGGAAAGGGGTAGTTG,,  
6476,H37989,,20,59,GAAAGGGGTAGTTGAGTAAG,,  
6477,H37989,,20,53,GGTAGTTGAGTAAGACGGCT,,  
65 6478,H37989,,20,47,TGAGTAAGACGGCTAAGGGA,,  
6479,H37989,,20,41,AGACGGCTAAGGGAACAG,,  
6480,H37989,,20,35,CTAAGGGAACAGAGAGCCT,,  
6481,H37989,,20,29,GAAGTGAAGCCTGAGGTG,,  
6482,H37989,,20,23,AGAAGCCTGAGGTGATGGGG,,  
70 6483,H37989,,20,17,CTGAGGTGATGGGGCTCTNC,,  
6484,H37989,,20,11,TGATGGGGCTCTNCTTAGGC,,  
6485,H37989,,20,5,GGCTCTNCTTAGGCCTCCNC,,  
(GENBANK ACCESSION NO. AA486238)  
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75 GGCTATTAGATCACTAGCACTGCTTTACCGCTCCTCATCGCCAAACACCCCATGCTCTGTGGCCTTCTTACACTTCTCAGAGGGCAGA



GTGGCAGCCGGGCACCCCTACAGAACTCAGAGGGCAGAGTGGCAGCCAGGCCACATGTCTCTCAAGTACCTGTCCCCTCGCTCTG  
GTGATTATTTCTTGCAGAATCACACACGACCATCCCGGCAGTCATGGTTTTGCTTTAGTTTTCCAAGTCCGTTTCAGTCCCTTCC  
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(SEQ ID NO: 6486)

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6487,AA486238,,20,388,AAAAGGGATCTTGGCAAGTG,,  
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6489,AA486238,,20,376,GGCAAGTGGGAAACTGCTCG,,

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6490,AA486238,,20,370,TGGGAAACTGCTCGCCACTG,,  
6491,AA486238,,20,364,ACTGCTCGCCACTGCAGAAT,,  
6492,AA486238,,20,358,CGCCACTGCAGAAATTTCTTC,,  
6493,AA486238,,20,352,TGCAGAAATTTCTTCAGACCA,,  
6494,AA486238,,20,346,ATTTCTTCAGACCAAGGAAG,,  
6495,AA486238,,20,340,TCAGACCAAGGAAGGGAAGT,,

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6496,AA486238,,20,334,CAAGGAAGGGACTGAAACGG,,  
6497,AA486238,,20,328,AGGGACTGAAACGGACTTGG,,  
6498,AA486238,,20,322,TGAAACGGACTTGGAAAAC,,  
6499,AA486238,,20,316,GGACTTGGAAAACATAAGCA,,  
6500,AA486238,,20,310,GGAAAACATAAGCAAAACCA,,

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6501,AA486238,,20,304,CTAAAGCAAAACCATGACTG,,  
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6503,AA486238,,20,292,CATGACTGCCGGGATGGTCT,,  
6504,AA486238,,20,286,TGCCGGGATGGTCTCGTGTG,,  
6505,AA486238,,20,280,GATGGTCTCGTGTGGTGATT,,

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6506,AA486238,,20,274,CTCGTGTGGTGATTCTGCA,,  
6507,AA486238,,20,268,TGGTGATTCTGCAAGAAATA,,  
6508,AA486238,,20,262,TTCTGCAAGAAATAATCACC,,  
6509,AA486238,,20,256,AAGAAATAATCACCAGAGCG,,  
6510,AA486238,,20,250,TAATCACCAGAGCGAGGGGA,,

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6511,AA486238,,20,244,CCAGAGCGAGGGGACAGGTA,,  
6512,AA486238,,20,238,CGAGGGGACAGGTACTTGAG,,  
6513,AA486238,,20,232,GACAGGTACTTGAGAGACAT,,  
6514,AA486238,,20,226,TACTTGAGAGACATGTGGGC,,  
6515,AA486238,,20,220,AGAGACATGTGGGCCTGGCT,,

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6516,AA486238,,20,214,ATGTGGGCCTGGCTGCCACT,,  
6517,AA486238,,20,208,GCCTGGCTGCCACTCTGCCC,,  
6518,AA486238,,20,202,CTGCCACTCTGCCCTCTGAG,,  
6519,AA486238,,20,196,CTCTGCCCTCTGAGTTTCTG,,  
6520,AA486238,,20,190,CCTCTGAGTTTCTGTAGGGT,,

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6521,AA486238,,20,184,AGTTTCTGTAGGGTGCCCGG,,  
6522,AA486238,,20,178,TGTAGGGTGCCCGGCTGCCA,,  
6523,AA486238,,20,172,GTGCCCGGCTGCCACTCTGC,,  
6524,AA486238,,20,166,GGCTGCCACTCTGCCCTCTG,,  
6525,AA486238,,20,160,CACTCTGCCCTCTGAGAAGT,,

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6526,AA486238,,20,154,GCCCTCTGAGAAGTGTAAAG,,  
6527,AA486238,,20,148,TGAGAAGTGTAAAGAGGCCA,,  
6528,AA486238,,20,142,GTGTAAGAAGGCCACAGAGC,,  
6529,AA486238,,20,136,GAAGGCCACAGAGCATGGGG,,  
6530,AA486238,,20,130,CACAGAGCATGGGGGTGTTG,,

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6531,AA486238,,20,124,GCATGGGGGTGTTGGCGATG,,  
6532,AA486238,,20,118,GGGTGTTGGCGATGAGGAGC,,  
6533,AA486238,,20,112,TGGCGATGAGGAGCGGTAAA,,  
6534,AA486238,,20,106,TGAGGAGCGGTAAAGCAGTG,,  
6535,AA486238,,20,100,GCGGTAAAGCAGTGCTAGTG,,

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6536,AA486238,,20,94,AAGCAGTGCTAGTGATCTAA,,  
6537,AA486238,,20,88,TGCTAGTGATCTAATAGCCA,,  
6538,AA486238,,20,82,TGATCTAATAGCCAAATACA,,  
6539,AA486238,,20,76,AATAGCCAAATACATTAACA,,  
6540,AA486238,,20,70,CAAAATACATTAACACGGACA,,

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6541,AA486238,,20,64,CATTAACACGGACACTGGAA,,  
6542,AA486238,,20,58,CACGGACACTGGAAGAGATT,,  
6543,AA486238,,20,52,CACTGGAAGAGATTAAGCGG,,  
6544,AA486238,,20,46,AAGAGATTAAGCGGATTTTA,,  
6545,AA486238,,20,40,TTAAGCGGATTTTAAGTCAT,,

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6546,AA486238,,20,34,GGATTTTAAGTCATCTCCTT,,  
6547,AA486238,,20,28,TAAGTCATCTCCTTTGCCAA,,  
6548,AA486238,,20,22,ATCTCCTTTGCCAAATGACA,,  
6549,AA486238,,20,16,TTTGCCAAATGACAACCAAA,,  
6550,AA486238,,20,10,AAATGACAACCAAACTAGGT,,

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6551,AA486238,,20,4,CAACCAAACTAGGTGTCCCC,,  
(GENBANK ACCESSION NO. AA504461)

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AAAATAATAACACAAATGCCAAATGTACACAGTGTACAACCTCTGAAGTGAAGGAGACCACGGGAATGGAAGTGGGT  
AGGGGTCGGGAGGATGGGCACACAGGCTGCTGTCTGACAGCCACACCTGGGTGCAGGCCACGTGTCTCACGGCCAAGGTAACCG

GGTGTCTCAGGCACCTTAATAATATTAAGGGTGACCGGTGACTCAGGCTCTGCCTCTGGGAAGTGGCATCATTTGGTGAATGAGTTT  
GGTCTCGGTGCCACC  
(SEQ ID NO: 6552)

5 6553,AA504461,,20,340,GGTGGCACCGAGACCAAACCT,,  
6554,AA504461,,20,334,ACCGAGACCAAACCTCATTCA,,  
6555,AA504461,,20,328,ACCAAACCTCATTACCAAAT,,  
6556,AA504461,,20,322,CTCATTACCAAATGATGCC,,  
6557,AA504461,,20,316,CACCAAATGATGCCACTTCC,,  
10 6558,AA504461,,20,310,ATGATGCCACTTCCCAGAGG,,  
6559,AA504461,,20,304,CCACTTCCCAGAGGCAGAGC,,  
6560,AA504461,,20,298,CCCAGAGGCAGAGCCTGAGT,,  
6561,AA504461,,20,292,GGCAGAGCCTGAGTCACCGG,,  
6562,AA504461,,20,286,GCCTGAGTCACCGGTACCCC,,  
15 6563,AA504461,,20,280,GTACCCGGTCACCCCTTAATA,,  
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6582,AA504461,,20,166,CCTCCCGACCCCTACCCACT,,  
35 6583,AA504461,,20,160,GACCCCTACCCACTTCCATT,,  
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6595,AA504461,,20,88,GGCATTGTGTTATTATTTT,,  
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50 6598,AA504461,,20,70,TTGCACTGTTTCTGTGCTG,,  
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55 6603,AA504461,,20,40,TGGGATCACAGGCCAGGGAA,,  
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60 6608,AA504461,,20,10,AATGAATGCCGGGGACAGAG,,  
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65 GAGCCTGACACCTCCACCTGCCACCCGCCCCGGGTGTAGTGGAACATGCAAAGCTCCGACGGTGGAGGCAGGGGTGGTCTGCTGCTG  
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75 6615,AA448400,,20,413,CCCTAGTAAGTCTCTCCATG,,

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25 6640,AA448400,,20,263,ACTGGGGTGGCGCCTGGCCG,,  
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35 6650,AA448400,,20,203,CACCAGCCAGGCTCTGTGCT,,  
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6677,AA448400,,20,41,ACCTGACCGTGGCGGGGCT,,  
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6679,AA448400,,20,29,GCGGGCTTGGCGTATCCGC,,  
65 6680,AA448400,,20,23,CTTGCGGTATCCGCCCCCAA,,  
6681,AA448400,,20,17,GTATCCGCCCCAATAAAAG,,  
6682,AA448400,,20,11,GCCCCAATAAAAGCAATTCT,,  
6683,AA448400,,20,5,AATAAAAGCAATTCCAACCT,,  
(GENBANK ACCESSION NO. AA480815)  
70 CGGTCAACCAATGTGTCACTCTCGCAGCTGCCACCCGACCATGACCATCTGCAAGGCCCGACCCCGGCCCTCCACCATCCCGGGA  
CCCCGCGTGTCTCGGTGCTGAGATCTTACCTTCGACCTCTCCCGAGCCCGAGCGCCCTGCGGGCGCCCCAGCGTCTNCGCG  
GGCACCGAAAGCGCAGCGCAGGGTTCTTACCTCGAGTGGTCCGGCGCAGTGCCTAGTCGAGGAACCGAACCCAGCCAAAAGG  
CTTCTCTTTCTGCTGCTCACCATCGTCTTCTGCCAGATCTGATGGCTGAAGAGGGTGTGCCGGC  
(SEQ ID NO: 6684)  
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6685,AA480815,,20,305,GCCGGCACACCTCTTCAGC,,  
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5 6689,AA480815,,20,281,AGGATCTGGCAGAAGACGAT,,  
6690,AA480815,,20,275,TGGCAGAAGACGATGGTGAG,,  
6691,AA480815,,20,269,AAGACGATGGTGAGCAGCAG,,  
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10 6694,AA480815,,20,251,AGAAAGAGAAGCCTTTTGGC,,  
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6710,AA480815,,20,155,CGCGANGACGCTGGGGCGCC,,  
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6712,AA480815,,20,143,GGGGCGCCCGCAGGGGCGCT,,  
6713,AA480815,,20,137,CCCGCAGGGGCGCTGCGGGC,,  
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6717,AA480815,,20,113,GGAGAGGGTCGAAGGTGAAG,,  
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35 6719,AA480815,,20,101,AGGTGAAGATCTCAGCGACC,,  
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6723,AA480815,,20,77,CACGCGGGTCCCGGATGG,,  
40 6724,AA480815,,20,71,GGGTCCCGGATGGTGAGG,,  
6725,AA480815,,20,65,CGGGATGGTGAGGGGGCCG,,  
6726,AA480815,,20,59,GGTGAGGGGGCCGGGGTTCG,,  
6727,AA480815,,20,53,GGGGCCGGGGTCCGGGCCT,,  
6728,AA480815,,20,47,CGGGGTCCGGGCCTGCAGGA,,  
45 6729,AA480815,,20,41,CGGGGCCTGCAGGATGGTCA,,  
6730,AA480815,,20,35,CTGCAGGATGGTCATGGTTCG,,  
6731,AA480815,,20,29,GATGGTCATGGTCGGGTGGC,,  
6732,AA480815,,20,23,CATGGTCGGGTGGCAGCTGC,,  
6733,AA480815,,20,17,CGGGTGCGAGCTGCGAGAGT,,  
50 6734,AA480815,,20,11,CGAGCTGCGAGAGTGACACA,,  
6735,AA480815,,20,5,GCGAGAGTGACACATGGTGA,,  
(GENBANK ACCESSION NO. AA102454)  
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55 CAGACACTAGTGGTGGTGAAATTTCATAAAAGTTTTTGAGGTGGCAACAGCTTATTTTGTCTTTATCATAATTGGTTTACAAATTGG  
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GGGGTCAAGAACTTGATTGTAAGGAGAACGATTTACTATTTACCAATCAATATTCTACAAAACCTGTCTCTTGGTTTNAACCCAAGC  
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60 (SEQ ID NO: 6736)  
  
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6738,AA102454,,20,563,GGTTAAAAATGCCAGCTGTT,,  
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65 6740,AA102454,,20,551,CAGCTGTTNTTCTACCCAAA,,  
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70 6820,AA102454,,20,71,TAGCAACATTACAGAAATTT,,  
6821,AA102454,,20,65,CATTACAGAAATTTGCCTT,,  
6822,AA102454,,20,59,AGAAATTTGCCTTGTGCC,,  
6823,AA102454,,20,53,TTTGCCTTGTGCCTTATCT,,  
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75 6825,AA102454,,20,41,CCTTATCTTCTCCAAATGT,,

6826,AA102454,,20,35,CTTCTTCCAAATGTAAGTT,,  
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6828,AA102454,,20,23,GTACTGTTAAATAAAAAATAA,,  
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5 6830,AA102454,,20,11,AAAAATAAANGGTTACCCCA,,  
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10 GAGAAATAATGAATAAAATCTTAATGTTTTCCCTCCACCGCCCTTTTTATTCTCCAAGATTAGGAATTACTACGGATTAGGTTTTT  
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(SEQ ID NO: 6832)  
  
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25 CCGCTATGTCTCCAGAAAGGAGAATACAGAACGAATCTGAAGACATCTACCCAGCAACCCCTACTGGATGATGACGTGAGCAGCGG  
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35 7533,R14663,,20,276,CAAAGANCTGGAGCATAT,,  
7534,R14663,,20,270,ANCCTGGAGCATATGGAATT,,  
7535,R14663,,20,264,GAGCATATGGAATTAACCG,,  
7536,R14663,,20,258,ATGGAATTAACCGNCATTTC,,  
7537,R14663,,20,252,TTAAACCGNCATTCTTAACC,,  
40 7538,R14663,,20,246,CGNCATTCTAACCAGAAAG,,  
7539,R14663,,20,240,TCCTAACCAGAAAGATAAGT,,  
7540,R14663,,20,234,CCCAGAAAGATAAGTGTATA,,  
7541,R14663,,20,228,AGATAAGTGTATAACAAAC,,  
7542,R14663,,20,222,GTGTTAAACAACTTATGA,,  
45 7543,R14663,,20,216,AAACAACTTATGAAGGGGA,,  
7544,R14663,,20,210,ACTTATGAAGGGGAAGTGGG,,  
7545,R14663,,20,204,GAAGGGGAAGTGGGTTTG,,  
7546,R14663,,20,198,GAAGTGGGTTTGGTGGAGG,,  
7547,R14663,,20,192,GGGTTTGGTGGAGGGGAATC,,  
50 7548,R14663,,20,186,GGTGGAGGGGAATCAGAAGG,,  
7549,R14663,,20,180,GGGGAATCAGAAGGGCATGA,,  
7550,R14663,,20,174,TCAGAAGGGCATGAAGGTCC,,  
7551,R14663,,20,168,GGGCATGAAGGTCCCTTGCT,,  
7552,R14663,,20,162,GAAGGTCCCTTGCTTTTGCT,,  
55 7553,R14663,,20,156,CCCTTGCTTTTGCTTTCCTT,,  
7554,R14663,,20,150,CTTTTGCTTTCCTTCTTAC,,  
7555,R14663,,20,144,CTTCTCTCCTTACCCAGAT,,  
7556,R14663,,20,138,TTCTTACCCAGATACCATC,,  
7557,R14663,,20,132,ACCCAGATACCATCGGACAT,,  
60 7558,R14663,,20,126,ATACCATCGGACATACTCTG,,  
7559,R14663,,20,120,TCGACATACTCTGTTTGGC,,  
7560,R14663,,20,114,ATACTCTGTTTGGCACTTGA,,  
7561,R14663,,20,108,TGTTTGGCACTTGAAGGCTC,,  
7562,R14663,,20,102,GCACTTGAAGGCTCTGGTAT,,  
65 7563,R14663,,20,96,GAAGGCTCTGGTATTTTGGC,,  
7564,R14663,,20,90,TCTGGTATTTTGGCAAAGCA,,  
7565,R14663,,20,84,ATTTTGGCAAAGCAATTATG,,  
7566,R14663,,20,78,GCAAAGCAATTATGGGAGGC,,  
7567,R14663,,20,72,CAATTATGGGAGGCCCAATC,,  
70 7568,R14663,,20,66,TGGGAGGCCCAATCCTAGAC,,  
7569,R14663,,20,60,GCCCAATCCTAGACGGCAAC,,  
7570,R14663,,20,54,TCCTAGACGGCAACTGGGGA,,  
7571,R14663,,20,48,ACGGCAACTGGGGACGAAGG,,  
7572,R14663,,20,42,ACTGGGACGAAGGAGTCTT,,  
75 7573,R14663,,20,36,GACGAAGGAGTCTTTGTGAC,,

7574,R14663,,20,30,GGAGTCTTTGTGACTAGATG,,  
7575,R14663,,20,24,TTTGTGACTAGATGGAAGTC,,  
7576,R14663,,20,18,ACTAGATGGAAGTCTTTCCC,,  
7577,R14663,,20,12,TGGAAGTCTTTCCCTCTGC,,  
5 7578,R14663,,20,6,TCTTTCCCTCTGCAGTCTG,,  
(GENBANK ACCESSION NO. R33355)  
TTTAAANNNTAAAGATTCTTTTATTATAATAATCTCCCTCCCTCCAACTCTCCCCAAAAATAATATCTCTCCCGCTTTGGGGAGA  
TTGGGGGGGTCTGTATCTTAGGGCCAGCCCTCTAGTGGGCCAGCCCCCTAGTGTTAAAAATAGGNCCCTAACCCCCCAGGGGTGA  
10 CCCCCGTGGGNGGGAATTTCAGGGACATCTGAGTGAGTGGGGGCCTAGTGTCAGTCTTGCCCCCAAGTCAGCCTGGGCCCCAG  
GCTTCTTAGGGAAGGGANGGGCACCCCCCTNCCCTGTTGCAAAATGCTTGCAAGTTCCTTAGTCAGTGTGAGCTGTTT  
(SEQ ID NO: 7579)

7580,R33355,,20,317,AAACAGCTGACACTGACTAA,,  
7581,R33355,,20,311,CTGACACTGACTAAGGAACT,,  
15 7582,R33355,,20,305,CTGACTAAGGAACTGCAAGC,,  
7583,R33355,,20,299,AAGGAACTGCAAGCATTGTC,,  
7584,R33355,,20,293,CTGCAAGCATTGCAACAGG,,  
7585,R33355,,20,287,GCATTGCAACAGGGNAGGG,,  
7586,R33355,,20,281,GCAACAGGGNAGGGGGGTGC,,  
20 7587,R33355,,20,275,GGGNAGGGGGGTGCCNTCC,,  
7588,R33355,,20,269,GGGGGTGCCNTCCCTTCCC,,  
7589,R33355,,20,263,GCCNTCCCTTCCCTAAGAA,,  
7590,R33355,,20,257,CCCTTCCCTAAGAAGCCTGG,,  
7591,R33355,,20,251,CCTAAGAAGCCTGGGGGCC,,  
25 7592,R33355,,20,245,AAGCCTGGGGGCCAGGCTG,,  
7593,R33355,,20,239,GGGGGCCAGGCTGACTTGG,,  
7594,R33355,,20,233,CCAGGCTGACTTGGGGGCA,,  
7595,R33355,,20,227,TGACTTGGGGGCAAGACTT,,  
7596,R33355,,20,221,GGGGGCAAGACTTGACACT,,  
30 7597,R33355,,20,215,CAAGACTTGACACTAGGCC,,  
7598,R33355,,20,209,TTGACACTAGGCCCACTC,,  
7599,R33355,,20,203,CTAGGCCCACTCACTCAG,,  
7600,R33355,,20,197,CCCCACTCACTCAGATGTCC,,  
7601,R33355,,20,191,TCACTCAGATGTCCCTGAAA,,  
35 7602,R33355,,20,185,AGATGTCCCTGAAATTTCCN,,  
7603,R33355,,20,179,CCCTGAAATTTCCNCCACG,,  
7604,R33355,,20,173,AATTCCNCCACGGGGGTC,,  
7605,R33355,,20,167,CNCCACGGGGGTACCCCT,,  
7606,R33355,,20,161,CGGGGTACCCCTGGGGGG,,  
40 7607,R33355,,20,155,TCACCCTGGGGGGTTAGGG,,  
7608,R33355,,20,149,CTGGGGGGTTAGGNCCTAT,,  
7609,R33355,,20,143,GGTTAGGNCCTATTTTAA,,  
7610,R33355,,20,137,GGNCCTATTTTAACTAG,,  
7611,R33355,,20,131,ATTTTAACTAGGGGGCT,,  
45 7612,R33355,,20,125,AACACTAGGGGGCTGGCCCA,,  
7613,R33355,,20,119,AGGGGGCTGGCCCACTAGGA,,  
7614,R33355,,20,113,CTGGCCCACTAGGAGGGCTG,,  
7615,R33355,,20,107,CACTAGGAGGGCTGGCCCTA,,  
7616,R33355,,20,101,GAGGGCTGGCCCTAAGATAC,,  
50 7617,R33355,,20,95,TGGCCCTAAGATACAGACCC,,  
7618,R33355,,20,89,TAAGATACAGACCCCCCAA,,  
7619,R33355,,20,83,ACAGACCCCCCAATCTCCC,,  
7620,R33355,,20,77,CCCCCAATCTCCCCAAAGC,,  
7621,R33355,,20,71,AATCTCCCCAAAGCGGGGAG,,  
55 7622,R33355,,20,65,CCCAAAGCGGGGAGGAGATA,,  
7623,R33355,,20,59,GCGGGGAGGAGATTTTATT,,  
7624,R33355,,20,53,AGGAGATATTTATTTGGGG,,  
7625,R33355,,20,47,TATTTATTTGGGGAGAGTT,,  
7626,R33355,,20,41,TTTGGGGAGAGTTTGGAGG,,  
60 7627,R33355,,20,35,GGAGAGTTTGGAGGGGAGGG,,  
7628,R33355,,20,29,TTTGGAGGGGAGGGAGAATT,,  
7629,R33355,,20,23,GGGAGGGGAGAATTTATTAA,,  
7630,R33355,,20,17,GGAGAATTTATTAATAAAAG,,  
7631,R33355,,20,11,TTTATTAATAAAAGAATCTT,,  
65 7632,R33355,,20,5,AATAAAAGAATCTTANNTT,,  
(GENBANK ACCESSION NO. T64626)  
CTCAGGTGAGACCAGATTGTGTCATTTGGCTCCACCTTCATCTTGAGANCAAGCTGATCTCAGATTGCCAAGAACTAGAAGCCACT  
TGCACGGTGTGGCCAGAGCTCAGCTGGATGAGAGGCTGAGATGGGTGGCCAGCTTGTATACAGTCCCTGAACTGAGCTGTTTACA  
GACTGGGGAGGCTCCACCCAGAAGGCTTTTCACTTGTACTGCTGGGAGTGACTGGGAAAACTCCTTCCTGCTGCTGAGTGGAG  
70 AGAGGCTCATCCGGCTTTGACCCACCATCCGTTGCAGAAGCCTCCAGGGAGCAGCAATCCTAAGAGTTGGGAGGCAGCCAAAGACC  
CCCTTCCTTTCAAAACCTTCCCGGAAGTNGTTT  
(SEQ ID NO: 7633)

7634,T64626,,20,362,AAAACNACTTCCGGGAAGGT,,  
75 7635,T64626,,20,356,ACTTCCGGGAAGGTTTTGAA,,

7636,T64626,,20,350,GGGAAGGTTTTGAAAGGAAA,,  
7637,T64626,,20,344,GTTTTGAAAGGAAAGGGGGT,,  
7638,T64626,,20,338,AAAGGAAAAGGGGGTCTTGCG,,  
7639,T64626,,20,332,AAGGGGGTCTTGCTGCCTC,,  
5 7640,T64626,,20,326,GTCTTGCTGCCTCCCAACT,,  
7641,T64626,,20,320,GCTGCCTCCCAACTCTTAGG,,  
7642,T64626,,20,314,TCCCAACTCTTAGGATTGCT,,  
7643,T64626,,20,308,CTCTTAGGATTGCTGCTCCC,,  
7644,T64626,,20,302,GGATTGCTGCTCCCTGGAGG,,  
10 7645,T64626,,20,296,CTGCTCCCTGGAGGCTTCTG,,  
7646,T64626,,20,290,CCTGGAGGCTTCTGCAACGG,,  
7647,T64626,,20,284,GGCTTCTGCAACGGATGGTG,,  
7648,T64626,,20,278,TGCAACGGATGGTGGGTCAA,,  
7649,T64626,,20,272,GGATGGTGGGTCAAAGCCGG,,  
15 7650,T64626,,20,266,TGGGTCAAAGCCGGATGAGG,,  
7651,T64626,,20,260,AAAGCCGGATGAGGCCTCTC,,  
7652,T64626,,20,254,GGATGAGGCCTCTCTCCACT,,  
7653,T64626,,20,248,GGCCTCTCTCCACTCAGCAG,,  
7654,T64626,,20,242,TCTCCACTCAGCAGCAGGGA,,  
20 7655,T64626,,20,236,CTCAGCAGCAGGGAAGGAGT,,  
7656,T64626,,20,230,AGCAGGGAAGGAGTTTTTCC,,  
7657,T64626,,20,224,GAAGGAGTTTTTCCCACTCA,,  
7658,T64626,,20,218,GTTTTCCCACTCACTCCCA,,  
7659,T64626,,20,212,CCCACTCACTCCCACTCAGAG,,  
25 7660,T64626,,20,206,CACTCCCACTCAGAGTACAAA,,  
7661,T64626,,20,200,CAGCAGAGTACAAATGAAAG,,  
7662,T64626,,20,194,AGTACAAATGAAAGCCTTCT,,  
7663,T64626,,20,188,AATGAAAGCCTTCTGGGTGG,,  
7664,T64626,,20,182,AGCCTTCTGGGTGGAGCCTC,,  
30 7665,T64626,,20,176,CTGGGTGGAGCCTCCCCAGT,,  
7666,T64626,,20,170,GGAGCCTCCCCAGTCTCTGA,,  
7667,T64626,,20,164,TCCCCAGTCTCTGTAACAGC,,  
7668,T64626,,20,158,GTCTGTGTAACAGCTCAGTT,,  
7669,T64626,,20,152,TAAACAGCTCAGTTCAGGGA,,  
35 7670,T64626,,20,146,GCTCAGTTCAGGGAAGTGA,,  
7671,T64626,,20,140,TTCAGGGAAGTGTATACAAG,,  
7672,T64626,,20,134,GACTGGTATACAAGCTGGCC,,  
7673,T64626,,20,128,TATACAAGCTGGCCACCCAT,,  
7674,T64626,,20,122,AGCTGGCCACCCATCTCAGC,,  
40 7675,T64626,,20,116,CCACCATCTCAGCCTCTCA,,  
7676,T64626,,20,110,ATCTCAGCCTCTCATCCAGC,,  
7677,T64626,,20,104,GCCTCTCATCCAGCTGAGCT,,  
7678,T64626,,20,98,CATCCAGCTGAGCTCTGGCC,,  
7679,T64626,,20,92,GCTGAGCTCTGGCCACACCG,,  
45 7680,T64626,,20,86,CTCTGGCCACACCGTGCAAG,,  
7681,T64626,,20,80,CCACACCGTGCAAGTGGCTT,,  
7682,T64626,,20,74,CGTGCAAGTGGCTTCTAGTT,,  
7683,T64626,,20,68,AGTGGCTTCTAGTTTCTTGG,,  
7684,T64626,,20,62,TTCTAGTTTCTTGGCAATCT,,  
50 7685,T64626,,20,56,TTTCTTGGCAATCTGAGATC,,  
7686,T64626,,20,50,GGCAATCTGAGATCAGCTGN,,  
7687,T64626,,20,44,CTGAGATCAGCTGNTCTGCA,,  
7688,T64626,,20,38,TCAGCTGNTCTGCAAGATGA,,  
7689,T64626,,20,32,GNTCTGCAAGATGAAGGTGG,,  
55 7690,T64626,,20,26,CAAGATGAAGGTGGAGCCAA,,  
7691,T64626,,20,20,GAAGGTGGAGCCAAATGACA,,  
7692,T64626,,20,14,GGAGCCAAATGACACAATCT,,  
7693,T64626,,20,8,AAATGACACAATCTGGTCTC,,  
7694,T64626,,20,2,CACAATCTGGTCTCACCTGA,,  
60 (GENBANK ACCESSION NO. AA448261)  
TTTCAGAAAAGGATATTTTTTTTATTCAGTAAGTAACTGCAAAATAGGAAACCAGAGAGGGAGCCCCAGGCTGGGACAAATCATGGCTA  
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CTAGGGGCAGGGCCAGCCTTCCCTGGGACTGGGGTAGTCGGTCAACCCAGCCTGCCATGCCCCAGCCCTCTTCCCCACAAAGAGTA  
TCTTGGGGGAGGGGATCGTGGGCAGAACAGGAGGCAATGAGGATGAACATTGGCGCTGGTAGCAGCAGCAATGACGGATTGTCG  
65 AAGAATGGAACATTGAACA  
(SEQ ID NO: 7695)  
  
7696,AA448261,,20,344,TGTTCAATGTTCCATTCTTC,,  
7697,AA448261,,20,338,ATGTTCCATTCTTCGACAAT,,  
70 7698,AA448261,,20,332,CATTCTTCGACAATCCGTC,,  
7699,AA448261,,20,326,TCGACAATCCGTCATTGCTG,,  
7700,AA448261,,20,320,ATCCGTCATTGCTGCTGCTA,,  
7701,AA448261,,20,314,CATTGCTGCTGCTACACAGCG,,  
7702,AA448261,,20,308,TGCTGCTACACAGCGCCAAAT,,  
75 7703,AA448261,,20,302,TACCAGCGCCAAATGTTTCAT,,



7704,AA448261,,20,296,CGCCAAATGTTTCATCCTCAT,,  
7705,AA448261,,20,290,ATGTTTCATCCTCATTGCCTC,,  
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7707,AA448261,,20,278,ATTGCCTCCTGTTCTGCCCA,,  
5 7708,AA448261,,20,272,TCCTGTTCTGCCACGATCC,,  
7709,AA448261,,20,266,TCTGCCACGATCCCCCTCCC,,  
7710,AA448261,,20,260,CACGATCCCCCTCCCCAAGA,,  
7711,AA448261,,20,254,CCCCTCCCCCAAGATACTCT,,  
7712,AA448261,,20,248,CCCCAAGATACTCTTGTGG,,  
10 7713,AA448261,,20,242,GATACTCTTGTGGGGAAGA,,  
7714,AA448261,,20,236,CTTGTGGGGAAGAGGGGCT,,  
7715,AA448261,,20,230,GGGGAAGAGGGGCTGGGGCA,,  
7716,AA448261,,20,224,GAGGGGCTGGGGCATGGCAG,,  
7717,AA448261,,20,218,CTGGGCATGGCAGGCTGGG,,  
15 7718,AA448261,,20,212,CATGGCAGGCTGGGTGACCG,,  
7719,AA448261,,20,206,AGGCTGGGTGACCGACTACC,,  
7720,AA448261,,20,200,GGTGACCGACTACCCAGTC,,  
7721,AA448261,,20,194,CGACTACCCAGTCCCAGGG,,  
7722,AA448261,,20,188,CCCCAGTCCCAGGGAAGGCT,,  
20 7723,AA448261,,20,182,TCCCAGGGAAGGCTGGCCCT,,  
7724,AA448261,,20,176,GGAAGGCTGGCCCTGCCCT,,  
7725,AA448261,,20,170,CTGGCCCTGCCCTAGGATG,,  
7726,AA448261,,20,164,CTGCCCTAGGATGCTGCAG,,  
7727,AA448261,,20,158,CTAGGATGCTGCAGCAGAGT,,  
25 7728,AA448261,,20,152,TGCTGCAGCAGAGTGAGCAA,,  
7729,AA448261,,20,146,AGCAGAGTGAGCAAGGGGGC,,  
7730,AA448261,,20,140,GTGAGCAAGGGGGCCGAAT,,  
7731,AA448261,,20,134,AAGGGGGCCGAATCGACCA,,  
7732,AA448261,,20,128,GCCCGAATCGACCAATAAAG,,  
30 7733,AA448261,,20,122,ATCGACCAATAAGGGTGTAG,,  
7734,AA448261,,20,116,CATAAAGGGTGTAGGGGCCA,,  
7735,AA448261,,20,110,GGGTGTAGGGGCCACCTCCT,,  
7736,AA448261,,20,104,AGGGGCCACCTCCTCCCCCT,,  
7737,AA448261,,20,98,CACCTCCTCCCCCTGTTCTG,,  
35 7738,AA448261,,20,92,CTCCCCCTGTTCTGTTGGGG,,  
7739,AA448261,,20,86,CTGTTCTGTTGGGGAGGGGT,,  
7740,AA448261,,20,80,TGTTGGGGAGGGGTAGCCAT,,  
7741,AA448261,,20,74,GGAGGGGTAGCCATGATTG,,  
7742,AA448261,,20,68,GTAGCCATGATTTGTCCCAG,,  
40 7743,AA448261,,20,62,ATGATTTGTCCCAGCCTGGG,,  
7744,AA448261,,20,56,TGTCCCAGCCTGGGGCTCCC,,  
7745,AA448261,,20,50,AGCCTGGGGCTCCCTCTCTG,,  
7746,AA448261,,20,44,GGGCTCCCTCTCTGGTTTCC,,  
7747,AA448261,,20,38,CCTCTCTGGTTTCTTATTG,,  
45 7748,AA448261,,20,32,TGGTTTCTTATTGCACTTA,,  
7749,AA448261,,20,26,CCTATTTGCAGTTACTTGAA,,  
7750,AA448261,,20,20,TGCAGTTACTTGAATAAAAA,,  
7751,AA448261,,20,14,TACTTGAATAAAAAAATAT,,  
7752,AA448261,,20,8,AATAAAAAAATATCCTTTT,,  
50 7753,AA448261,,20,2,AAAAATATCCTTTTCTGGAA,,  
(GENBANK ACCESSION NO. R44202)  
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AAGTCATGATTGAGTCTAAAAAAGAACAATCCAGTGTTCAGAGAGGTTAGCATGTCAGGGCGCAGGCTCGGCCGAGGNTG  
TGCTTTGCATTTAGGGACACAGCCCGGAGCCGAGAGGTGACGAGGGAGCACGCTGGGCACCTTCAGTACCAGGGCTGGGTGAG  
55 AGAGCCCGGA  
(SEQ ID NO: 7754)

7755,R44202,,20,252,TCCGGGCTCTCTCACCAGC,,  
7756,R44202,,20,246,CTCTCTCACCAGCCCTGGT,,  
60 7757,R44202,,20,240,CACCCAGCCCTGGTACTGAA,,  
7758,R44202,,20,234,GCCCTGGTACTGAAGGTGCC,,  
7759,R44202,,20,228,GTACTGAAGGTGCCAGACG,,  
7760,R44202,,20,222,AAGGTGCCAGACGTGCTCC,,  
7761,R44202,,20,216,CCCAGACGTGCTCCCTGCTG,,  
65 7762,R44202,,20,210,CGTGTCTCCCTGCTGACCTTC,,  
7763,R44202,,20,204,CCCTGCTGACCTTCTGCGGC,,  
7764,R44202,,20,198,TGACCTTCTGCGGCTCCGGG,,  
7765,R44202,,20,192,TCTGCGGCTCCGGGCTGTGT,,  
7766,R44202,,20,186,GCTCCGGGCTGTGTCCCTAA,,  
70 7767,R44202,,20,180,GGCTGTGTCCCTAAATGCAA,,  
7768,R44202,,20,174,GTCCCTAAATGCAAAGCACA,,  
7769,R44202,,20,168,AAATGCAAAGCACANCTCG,,  
7770,R44202,,20,162,AAAGCACANCTCGCCGAGC,,  
7771,R44202,,20,156,CANCTCGCCGAGCCTGCGC,,  
75 7772,R44202,,20,150,CGCCGAGCCTGCCCTGAC,,

7773,R44202,,20,144,GCCTGCGCCCTGACATGCTA,,  
7774,R44202,,20,138,GCCCTGACATGCTAACCTCT,,  
7775,R44202,,20,132,ACATGCTAACCTCTCTGAAC,,  
7776,R44202,,20,126,TAACCTCTCTGAACTGCAAC,,  
5 7777,R44202,,20,120,CTCTGAACTGCAACACTGGA,,  
7778,R44202,,20,114,ACTGCAACACTGGATTGTTCT,,  
7779,R44202,,20,108,ACACTGGATTGTTCTTTTTT,,  
7780,R44202,,20,102,GATTGTTCTTTTTTAAGACT,,  
7781,R44202,,20,96,TCTTTTTTAAGACTCAATCA,,  
10 7782,R44202,,20,90,TTAAGACTCAATCATGACTT,,  
7783,R44202,,20,84,CTCAATCATGACTTCTTTAC,,  
7784,R44202,,20,78,CATGACTTCTTTACTAACAC,,  
7785,R44202,,20,72,TTCTTTACTAACACTGGCTA,,  
7786,R44202,,20,66,ACTAACACTGGCTAGCTATA,,  
15 7787,R44202,,20,60,ACTGGCTAGCTATATTATCT,,  
7788,R44202,,20,54,TAGCTATATTATCTTATATA,,  
7789,R44202,,20,48,TATTATCTTATATACTAATA,,  
7790,R44202,,20,42,CTTATATACTAATATCATGT,,  
7791,R44202,,20,36,TACTAATATCATGTTTTAAA,,  
20 7792,R44202,,20,30,TATCATGTTTTAAAAATATA,,  
7793,R44202,,20,24,GTTTTAAAAATATAAAATAG,,  
7794,R44202,,20,18,AAAATATAAAATAGAAATTA,,  
7795,R44202,,20,12,TAAAATAGAAATTAAGAATC,,  
7796,R44202,,20,6,AGAAATTAAGAATCTAAAAA,,  
25 (GENBANK ACCESSION NO. W81570)  
GCGACCGCTCGCGCCTCTCGANGGACAACTCGCACTTGCTCAACAAGGGCCCTGCCGCTTGGGTCNGACCTCNGATCATGAACGGGGC  
ACCTGCANCCGCGGCCCTGGTGCAATTGNTGGATGGCCGGGACTGCACAGTGGAGATGCCCATCCTGAAGGACGTGGCCACTGTG  
GCTTCTGCGACGCGCAGTCCACGCAGGAGATCCATGAGAAGGTCCTGAACGAGGGCTGTGGGGGGCCCTGATGTACCAACCATCACT  
CTCACCCAGGAGGACCTGGAGAGGTTCAAAGCCCTCCGCATCATCGTCCGGATTGGCAGTGGTTTTGACAACATCGACATCAAGTC  
30 GGCCGGGGATTTTAGGCATTTGCCGTCTGCAACGTGCCCGCGGCGTCTGTTGGGAGGAGACGGCCGACTTCGA  
(SEQ ID NO: 7797)

7798,W81570,,20,400,TCGAAGTCGGCCGTCTCCTC,,  
7799,W81570,,20,394,TCGGCCGTCTCCTCCCAACA,,  
35 7800,W81570,,20,388,GTCTCCTCCCAACAGAACGC,,  
7801,W81570,,20,382,TCCCAACAGAACGCCGCGGG,,  
7802,W81570,,20,376,CAGAACGCCGCGGGCACGTT,,  
7803,W81570,,20,370,GCCGCGGGCACGTTGCAGAA,,  
7804,W81570,,20,364,GGCACGTTGCAGAACGGCAA,,  
40 7805,W81570,,20,358,TTGCAGAACGGCAAATGCCT,,  
7806,W81570,,20,352,AACGGCAAATGCCTAAAATC,,  
7807,W81570,,20,346,AAATGCCTAAAATCCCCGGC,,  
7808,W81570,,20,340,CTAAAATCCCCGGCCGACTT,,  
7809,W81570,,20,334,TCCCCGGCCGACTTGATGTC,,  
45 7810,W81570,,20,328,GCCGACTTGATGTCGATGTT,,  
7811,W81570,,20,322,TTGATGTCGATGTTGTCAAA,,  
7812,W81570,,20,316,TCGATGTTGTCAAAACCACT,,  
7813,W81570,,20,310,TTGTCAAAACCACTGCCAAT,,  
7814,W81570,,20,304,AAACCACTGCCAATCCGGAC,,  
50 7815,W81570,,20,298,CTGCCAATCCGGACGATGAT,,  
7816,W81570,,20,292,ATCCGGACGATGATGCGGAG,,  
7817,W81570,,20,286,ACGATGATGCGGAGGGCTTT,,  
7818,W81570,,20,280,ATGCGGAGGGCTTTGAACCT,,  
7819,W81570,,20,274,AGGGCTTTGAACCTTCTCCAG,,  
55 7820,W81570,,20,268,TTGAACCTTCTCCAGGTCCTC,,  
7821,W81570,,20,262,TTCTCCAGGTCCTCCCTGGT,,  
7822,W81570,,20,256,AGGTCCTCCCTGGTGAGAGT,,  
7823,W81570,,20,250,TCCCTGGTGAGAGTGATGGT,,  
7824,W81570,,20,244,GTGAGAGTGATGGTGTGGTA,,  
60 7825,W81570,,20,238,GTGATGGTGTGGTACATCAG,,  
7826,W81570,,20,232,GTGTGGTACATCAGGGCCCC,,  
7827,W81570,,20,226,TACATCAGGGCCCCACAGC,,  
7828,W81570,,20,220,AGGGCCCCACAGCCTCGTT,,  
7829,W81570,,20,214,CCCACAGCCTCGTTTCAGGAC,,  
65 7830,W81570,,20,208,GCCTCGTTCAGGACCTTCTC,,  
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7832,W81570,,20,196,ACCTTCTCATGGATCTCCTG,,  
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7861,W81570,,20,22,GAGCAAGTGCAGTGTCCN,,  
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30 CCAGCCTGGCCAACATGGCGAAACCCCGTCTCTACTAAACATACAAAAATCAGTTGGGCATGGTGGCGTGTGCTGTAGTCCCAGC  
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7937,N58473,,20,554,GCCTAGTATTTTAGTTAGAG,,  
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40 7939,N58473,,20,542,AGTTAGAGATGAATTGCTTT,,  
7940,N58473,,20,536,AGATGAATTGCTTTGATGNG,,  
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40 8014,N58473,,20,92,TGGATTGTCTGTTAATTATC,,  
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45 8019,N58473,,20,62,TGCAGTGAGTAATTTGGGC,,  
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50 8024,N58473,,20,32,CTACATTCCTTATTTTCATC,,  
8025,N58473,,20,26,TCCTTATTTTCATCCAGAGT,,  
8026,N58473,,20,20,TTTTCATCCAGAGTATAATT,,  
8027,N58473,,20,14,TCCAGAGTATAATTAATGTC,,  
8028,N58473,,20,8,GTATAATTAATGTCTTAATA,,  
55 8029,N58473,,20,2,TTAATGTCTTAATATACCCA,,  
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70 TTGCNAAACAGCCCTGGGCACACTTGCTACAGCCCAAGGGCANGCAGGAGCAGCAGCTCTTCTTGCANGAGGGTG  
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75 8111,N55459,,20,219,AGAAGAGCTGCTGCTCCTGC,,



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8114,N55459,,20,201,GCNTGCCCGTGGGCTGTAGC,,  
5 8115,N55459,,20,195,CCGTGGGCTGTAGCAAGTGT,,  
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60 8440,AA001432,,20,5,ATGCAGTGTAGTCCTTAAAA,,  
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10 8460,H87536,,20,210,ACAAGGAAGGAATAAAGGGA,,  
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70 8510,AA664179,,20,551,GGAAGACCCGAGAGGAGCTA,,  
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5 8520,AA664179,,20,491,GTACCACACAGTCTGCTGA,,  
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8596,AA664179,,20,35,AGCAGGGTACCCCTTTGGGGA,,  
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15 ACTACACCCAAAGTGTCTACAACCACATGCAGAAGCACAAGCCCTACCCGTCATCGAGGAGTTCTCTGGGTGCGNGATGGCAGGCT  
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(SEQ ID NO: 8653)

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## RANTES

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14121 CTGACAATCCCTGCGCAGTC  
14122 CTGCGCAGTCAATGCCTCTT  
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14128 CTCTTCTCCTCCAGCGTCA  
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14134 CCCCCTTGACTCCTCCTCGG  
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14137 TGGGCTCTGCCGGATGGCGC  
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14143 CTCTGGGCATCTGGGTGGA  
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14146 CCAGGTCTCCACAATGGGT  
14147 CACAATGGGTGCACAATGTA  
14148 GCACAATGTAGTCAATAAAA  
14149 GTCAATAAAACCCACCTGAG  
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14153 TGCTTGTACACATGGGGCT  
14154 ACATGGGGCTGATTTCCATG  
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14157 GCTCTCGGTACCCTGCTGG  
14158 ACCCTGCTGGAAGAACTCGG  
14159 AAGAACTCGGCCATGATGCG  
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14161 GTCTGTCCACTGGCGGTACA  
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14163 GCTCCAGCGGCTTGGTGGGG  
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70 14165 TTGCTGAGGTGGGCACAGTG  
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75 14170 GGAGTAGTTATCTAGCAGGA



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14184 GCCGCTGGCGCTTGTGAGG  
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14186 TTCTGGAAGATGTCGAGTT  
14187 TGTGCGAGTTGTCTCCTGC  
14188 GTCCTCCTGCAGCAGCTTGA  
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20 14190 AGCCACGCGCCAGGTGGTGA  
14191 CAGGTGGTGATTCTCGAGCA  
14192 TTCTCGAGCACCGACTCATC  
14193 CCGACTCATCGTTGTACATG  
14194 GTTGACATGAGCGCCAGCT  
25 14195 AGCGCCAGCTCCGAATTGGT  
14196 CCGAATTGGTGTGATGAGG  
14197 GTTGATGAGGAAGTGGTTGG  
14198 AACTGGTTGGAGACCCAGG  
14199 AGACCCAGGGTGATCCACA  
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14202 CAGCCGCGAAGAGGGCGGCG  
14203 GAGGGCGGCGAGAATCTCCA  
14204 AGAATCTCCAGGTCCGTGAA  
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14211 CGTCAGCTGCGTGCAGGCTG  
14212 GTGCAGGCTGTTATGGTAGG  
14213 TTATGGTAGGCCACGTCAGC  
14214 CCACGTCAGCGTGGTAGTGA  
45 14215 GTGGTAGTGATCCTCCAGCG  
14216 TCCTCCAGCGTCAGCATGTA  
14217 TCAGCATGTATGTCACCATC  
14218 TGTCAACATCGTGTCCACCG  
14219 GTGTCCACCGGGATGCGGAA  
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14221 TTCTTCAGCAGGTCCCGCT  
14222 AGGTCCCGCTCCTGGAATAT  
14223 CCTGGAATATCATGTACATG  
14224 CATGTACATGATGCAGGTGA  
55 14225 ATGCAGGTGAGTGAGCGGCC  
14226 GTGAGCGGCCTCCAGCGTAA  
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14228 TCCGACACGCAAAAAGATGTT  
14229 AAAAGATGTTTCAAGCCCCAC  
60 14230 CAGGCCCCACTGTTCAGGT  
14231 TTGTTCAAGTTCTCCAGTTC  
14232 TCTCCAGTTCTTGGGCCAGG  
14233 TTGGGCCAGGAGCTCTTCTT  
14234 AGCTCTTCTTGATCGGTCTT  
65 14235 GATCGGTCTTCAACCCAAAT  
14236 CACCCCAAATCGGGGAATGT  
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14238 TAGAGTTGTTTCAAGGCTGTTA  
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70 14240 CTATGCATCAACTTTTTCAA  
14241 ACTTTTTCAACCCCTGTGATT  
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14243 TGGGACATGGGCTGTAAGTG  
14244 GCTGTAAGTGTGTACAGGG  
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 14253 GGATCTCCACTTCATTCTGT  
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 10 14255 TTGTCCAGGAATGTTGTGGA  
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 14259 TTCCGGACCTGCTCATTCT  
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 14263 GTTCAACATCCTTTTGAAC  
 14264 CTTTTGAACCTGGTCCCACCA  
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 14266 GCCCACCAGCCAAGGCTTAG  
 14267 CAAGGCTTAGAGCAGGTCTC  
 14268 AGCAGGTCTCGCAGAAGAAA  
 14269 GCAGAAGAAATCCACCAAGG  
 25 14270 TCCACCAAGGGCATCTTGGA  
 14271 GCATCTTGGAGACTTAGCCC  
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 14273 TCTTCAGCAGGTCCCCTCTG  
 30 14274 AACTGTTGGAGACCCAGG  
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 14276 GCTGAGGTTCTGGAAGAT  
 14277 GTGGCCAGCACCATGTC  
 14278 TTCTTGGTCTCCACCATGGTCTT  
 35 14279 CAGCGGCTTGGTGGGGTTGCT  
 14280 GTCCACTGGCGGTACAG  
 14281 TGCTTGTCACACATGGG  
 14282 GTCCACTGGCGGTACAGCT  
 14283 TGTGCTTGTCACACATGGGGCT  
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 14285 CTTGGTGGGGTTGCTCAG  
 14286 AGAGTCAGTTCAAACCTG  
 14287 AAGACCCCATTTGTTC  
 14288 TCTGCCCATGTCTCCCA  
 45 14289 AACTTGTTGGAGGCCATCTC  
 14290 CGGTCCGTCCACTGGCGGTACAG  
 14291 TGCTTGTCACACATGGG  
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 50 14293 TTTTTTTTCTTTTTGAGA  
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 14300 GCTCACTGCAACCTCCACCT  
 14301 ACCTCCACCTCTGAATTCA  
 14302 CCTGAATTCAAGTGATTCTC  
 60 14303 AGTGATTCTCTGCTCAGC  
 14304 CTGCCTCAGCCTCCCAAGTA  
 14305 CTCCCCAGTAGCTGGGATTA  
 14306 GCTGGGATTACAGGCACCCG  
 14307 CAGGCACCCGCCACCATGCC  
 65 14308 CCACCATGCCAGCCAAATTT  
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 14310 TTGTATTTTAGTAGAGATG  
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 14314 GGCTGGTCTCGAACTCCTAA  
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 14316 CCTCAGGTGATCCACCTGCC  
 14317 TCCACCTGCCTCAGCCTCCC  
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14319 AAAGTGCTGGGATTATAGGC  
14320 GATTATAGGCATGGGCCACT  
14321 ATGGGCCACTGTGCTCGGCC  
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14323 TCAGAGCCCCGTCTCTTCC  
14324 GTCTCTTTCCTTCTCTCTC  
14325 TTTCTTCTCTTTTCTTTT  
14326 TTTTCTTTTATTTTAGAC  
14327 ATTTTACAGGATCTTGC  
10 14328 AGGATCTTGCTGTGTGCC  
14329 TGTGTTGCCAGGCTGGAGT  
14330 AGGCTGGAGTGCAGTATGC  
14331 GCAGTGATGCAGTCATAGCT  
14332 AGTCATAGCTCTTTCAGCC  
15 14333 CTCTTCAGCCTCCAACCTCT  
14334 TCCAACCTCCTGGGCTCAAGC  
14335 GGGCTCAAGCGATCCCCCTT  
14336 GATCCCCCTTGTCTCAACCT  
14337 GTCTCAACCTTCTGAGTAGC  
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14339 TGGGATTCTCAGGTGCACAC  
14340 AGGTGCACACCACCATGCCT  
14341 CACCATGCCTGGCTAATTTT  
14342 GGCTAATTTTTTTTTTCAGA  
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14344 GATGGTGGGGTCTTGCTAT  
14345 GTCTTGCTATGTTGCCAGG  
14346 GTTGCCAGGCTGGTCTCAA  
14347 CTGGTCTCAAACTCCTGAGC  
30 14348 ACTCCTGAGCTTAAGCAGTC  
14349 TTAAGCAGTCTCCACCTC  
14350 CTCCACCTCAGCCTCCCAA  
14351 AGCCTCCCAAAGTACCGGGA  
14352 AGTACCGGATTACAGGCAT  
35 14353 TTACAGGCATAAGCCACTAT  
14354 AAGCCACTATGCCTTGCCCA  
14355 GCCTTGCCAGCCCTTCTTT  
14356 GCCCTTCTTTCTGCTCCTC  
14357 TCTGCTCCTCTTCTGCCCC  
40 14358 TTCCTGCCCCCTACCGTAGT  
14359 CTACCGTAGTTTCAGAAACA  
14360 TTCAGAAACAAACTGGGTA  
14361 AAAGTGGGTATGAGTGAAGC  
14362 TGAGTGAAGCTTTGGTGCTG  
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14364 AAAATTTTCCCACTCACAT  
14365 CCACTCACATTTCCATGCTC  
14366 TTCCATGCTCTTGACAGAG  
14367 TTGCAGAGAGCCGCTTGTA  
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14369 GAGGAAGACAGGGAGATGCC  
14370 GGGAGATGCCTTTGGGATGG  
14371 TTTGGGATGGTCTCCTGACT  
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55 14373 CCCCACCCTTTGTGAGGGC  
14374 TGTGCAGGGCTACTACAGAG  
14375 TACTACAGAGGCAGAAAGCT  
14376 GCAGAAAGCTGGCCGAAGT  
14377 GGCCCGAAGTAGATGAGCAA  
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14381 AAATAATTAAGTGACAGATG  
14382 GTGACAGATGTGACTCAAGA  
65 14383 TGA CTCAAGAGTGACCACTG  
14384 GTGACCACTGGAGAGGGTGG  
14385 GAGAGGGTGGACTAGAGGCT  
14386 ACTAGAGGCTCCAGCAGACA  
14387 CCAGCAGACAGCACCTCTCC  
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14389 TCACAGGGATAGAAGCCCAG  
14390 AGAAGCCCAGGAGAAAGACA  
14391 GAGAAAGACACCAGGGCATC  
14392 CCAGGGCATCGTAAGAGGCT  
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14395 GAGCTCTTTTAGGCAAGTCT  
14396 AGGCAAGTCTAGGGTCAGAG  
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14400 CCAATTAGACCCTGGGAGCC  
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14406 GAAAGTGAAGCAGGAGCCAC  
14407 CAGGAGCCACATGGAGCCTC  
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14414 CCCTGCAGTTACGCAGGGC  
14415 CACGCAGGGCTGGCCCTAAG  
14416 TGGCCCTAAGTCTCTGGTT  
14417 TCCTCTGGTTGTGAGGGGT  
25 14418 GTCGAGGGGTAAATCCCCAG  
14419 AAGTCCCAGGGTCTGGGCC  
14420 GGTCTGGGCCGGCTTCAGGG  
14421 GGCTTCAGGGGACAGGAGTT  
14422 GACAGGAGTTCAGTGTGAGG  
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14425 GCCTCTTTGGCTAAAGCTGT  
14426 CTAAAGCTGTCTCTTCCCCC  
14427 CTCTTCCCCTCTCTTCTT  
35 14428 TCCTCTTCTTCTCTCTCATC  
14429 CCTCTCATCTCTTCTCT  
14430 CTCTTCTCTGCCTCTCTCA  
14431 GCCTCTCCAGAGTCAGTTC  
14432 GAGTCAGTTCAAACTGGAAT  
40 14433 AAAC TGGAATCTGTGAGGCC  
14434 CTGTGAGGCCGTCCCGCTC  
14435 CGTCCCGCTCGGGGTGGTG  
14436 GGGGTGGTGAGGTCTGAGG  
14437 AGGTCTGAGGGACTTCGGGG  
45 14438 GACTTCGGGGATCTTGCTC  
14439 GATCTTGCTCTGGTACCACT  
14440 TGGTACCACTCTCGATTGTC  
14441 CTCGATTGTCTCCAGCGTG  
14442 CTCCAGCGTGTCCAGAGGT  
50 14443 TCCAGCAGGTCTGTGCATC  
14444 CCTGTGCATCTGGGTGGACC  
14445 TGGGTGGACCAGGTGAGCCC  
14446 AGGTGAGCCCAAGTCTCCCA  
14447 AAGTCTCCACAGTGGGTGA  
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14449 GCAATGTAGTCAATGAAACC  
14450 CAATGAAACCCACCTGGGAC  
14451 CACCTGGGACTTCTCCACTG  
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60 14453 AGGCCGTATGCTTGTCACAC  
14454 CTTGTACACATGGGACTGA  
14455 ATGGGACTGATGTCCAGGCC  
14456 TGTCCAGGCCGACTCACGC  
14457 CGACTCACGCTCGCGGTCTC  
65 14458 TCGCGGTCTCCCTGCTGGAA  
14459 CCTGCTGGAAGAACTCGGCC  
14460 GAACTCGGCCATGATGCGGT  
14461 ATGATGCGGTCCGTCCACTG  
14462 CCGTCCACTGGCGGTACAGG  
70 14463 GCGGTACAGGGGCAGCGGCT  
14464 GGCAGCGGCTTGGTGGGGTT  
14465 TGGTGGGGTTGCTCAGATCA  
14466 GCTCAGATCAGCACAGTGCA  
14467 GCACAGTGCACAGGTTCTG  
75 14468 CCAGGTTCTGCAAGACCTGG

14469 CAAGACCTGGATTCCGGTCGG  
14470 ATTCGGTCGGAATAGTTGTC  
14471 AATAGTTGTCCAGGAGGAGG  
5 14472 CAGGAGGAGGACACCGAGGC  
14473 ACACCGAGGCTTGTACCTT  
14474 TTGTACCTTCTTGGTCTCC  
14475 CTTGGTCTCCACCATGGTCT  
14476 ACCATGGTCTTGAGGTCGGC  
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14481 GGCCAGCACCATGTCAATGA  
14482 ATGTCAATGACCATCCTGCG  
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14484 CAGACTCAGTCGCTGCTTGG  
14485 CGCTGCTTGGCGCTGAGGTT  
14486 CGCTGAGGTTCTGGAAGATA  
14487 CTGGAAGATATCGCAGTTCT  
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14489 CTGCCTGCAGCAGCTTGAAG  
14490 CAGCTTGAAGCCACAGCCA  
14491 CCCACAGCCAGGTGATGGTT  
14492 GGTGATGGTTCTCCAGCACC  
25 14493 CTCCAGCACCGAGGCGTCGT  
14494 GAGGCGTCGTTGTACATAAG  
14495 TGTACATAAGCGCCACGTCT  
14496 CGCCACGTCTGAGTTGGTGT  
14497 GAGTTGGTGTAAATCAGAAA  
30 14498 TAATCAGAACTGGTTGGAG  
14499 CTGGTTGGAGACCCAGGAT  
14500 ACCCCAGGATGGTCCACGTC  
14501 GGTCCACGTCGTGGATGGCG  
14502 GTGGATGGCGCTTGCAAAGA  
35 14503 CTTGCAAAGAGGGCAGCCAG  
14504 GGGCAGCCAGGATTCCAAG  
14505 GATTTCCAAGTCTGTGAACA  
14506 TCTGTGAACACAGCCTCGAG  
14507 CAGCCTCGAGGGCGGGCGTA  
40 14508 GGCGGGCGTAGCCAGCAGCA  
14509 GCCAGCAGCACATGCGTGGA  
14510 CATGCGTGGACTGGGCCACG  
14511 CTGGGCCACGTCGGCGGCAT  
14512 TCGGCGGCATGTAGGCTGTT  
45 14513 GTAGGCTGTTGTGGTAGGCC  
14514 GTGGTAGGCCACATTGGCGT  
14515 ACATTGGCGTGGTAGTGACC  
14516 GGTAGTGACCCTCCAGCATC  
14517 CTCCAGCATCAGCAGGTAGG  
50 14518 AGCAGGTAGGTGGCCAGTGT  
14519 TGGCCAGTGTGTCTGCTGGG  
14520 GTCTGCTGGGATCTGGAATG  
14521 ATCTGGAATGTCTTCAGCAG  
14522 TCTTCAGCAGGTCCCGTCC  
55 14523 GTCCCGCTCCTGAAAAATGC  
14524 TGAAAAATGCTGAATATGAT  
14525 TGAATATGATAGCTGTGAGG  
14526 AGCTGTGAGGGGCCGTTCC  
14527 GGCCGGTTCCCACTTACGTC  
60 14528 CACTTACGTCCGCCACCTTG  
14529 CGCCACCTTGAACACATCAA  
14530 AACACATCAAGTCCCACTT  
14531 GTCCCACTTGTGGTGTCT  
14532 GTTGGTGTCTCTAGCTCCT  
65 14533 TCTAGCTCCTTGGCCAGTTG  
14534 TGGCCAGTTGCTCCTCCTGG  
14535 CTCCTCCTGGTCAGTCTGGA  
14536 TCAGTCTGGACCCCAAAGCG  
14537 CCCCAAAGCGTGGGACAGTG  
70 14538 TGGGACAGTGGCTGAGGAGA  
14539 GCTGAGGAGAGGCTGGCACT  
14540 GGCTGGCACTGTGGCAGAGC  
14541 GTGGCAGAGCCCATGTAGGC  
14542 CCATGTAGGCCACTGATCCG  
75 14543 CACTGATCCGGGACATGGGC

14544 GGACATGGGCTGTGGGGCCT  
14545 TGTGGGGCCTCCTCAGCGGT  
14546 CCTCAGCGGTACCTTGGGC  
5 14547 CACCTTGGGCAGCTCCACCT  
14548 AGTCCACCTCGGTCTGCTG  
14549 CGGTCTGCTGGTCCAGGAAG  
14550 GTCCAGGAAGGTCCGGGAGA  
14551 GTCCGGGAGATGTA CT CGGA  
14552 TGTACTCGGACACCTGGTTC  
10 14553 CACCTGGTTCCCGGAGCGGC  
14554 CCGGAGCGGCTGGTTTCGGA  
14555 TGGTTTCGGACAGGTGGGTC  
14556 CAGGTGGGTCAACTCCCGGT  
14557 AACTCCCGGTT CAGGATCCG  
15 14558 TCAGGATCCGCTTGA ACTTG  
14559 CTTGAACTTGT TGGAGGCCA  
14560 TTGGAGGCCATCTCCCCAC  
14561 TCTCCCCACCGAGTGCCGG  
14562 CGAGTGCCGGGTCTGCAGCG  
20 14563 GTCTGCAGCGTCTCCAACTG  
14564 TCTCCAACTGATCCAGGCAC  
14565 ATCCAGGCACCA GTCCAGCT  
14566 CAGTCCAGCTCGTCTAGCGT  
14567 CGTCTAGCGTCTCCAATGCC  
25 14568 CTCCAATGCCAGCTTCTGCC  
14569 AGCTTCTGCCCGGTGTCCTC  
14570 CCGTGTCTCTGCAGGAGGG  
14571 TGCAGGAGGGAGCTGATTGC  
14572 AGCTGATTGCTGGATGAAGG  
30 14573 TGGATGAAGGGTTTCCGACG  
14574 GTTTCGACGGGTCCCTGCT  
14575 GGTCCCTGCTTGGCTGCTCC  
14576 TGGCTGCTCCTAGGCATTGC  
14577 TAGGCATTGCTGGCGGGCAA  
35 14578 TGGCGGGCAAGGCGCGCCAC  
14579 GGGCCGCCACGTTGCTCCGA  
14580 GTTGCTCCGAACGGTCCGCA  
14581 ACGGTCCGCAGACTGGCCAG  
14582 GACTGGCCAGGACCTGGGCA  
40 14583 GACCTGGGCAAAGGGCGTCA  
14584 AAGGGCGTCACAATCATGTC  
14585 CAATCATGTCTCTCCATGT  
14586 CTCTCCATGTAGGTCTGCTGG  
14587 AGGTCGCTGGCCACAGAGGA  
45 14588 CCACAGAGGAGTCCGAGAC  
14589 GTTCCGAGACATGGCCTTGG  
14590 ATGGCCTTGGGCGAGAGTTC  
14591 GCGAGAGTT CATAGTCGCTA  
14592 ATAGTCGCTATCTGAGCGGT  
50 14593 TCTGAGCGGTACAGGAAGGA  
14594 ACAGGAAGGACTCGCGCCGC  
14595 CTCGCGCCGCTGGCTGTGCG  
14596 TGGCTGTGCGGGA CTGGAGC  
14597 GGA CTGGAGCCTGCATAATC  
55 14598 CTGCATAATCCGCGCCAGGC  
14599 CGGCCAGGCCAGGGCTGGA  
14600 CAGGGCTGGACTGAGGGTCC  
14601 CTGAGGGTCCAGGGCCCTCC  
14602 AGGGCCCTCCTCCACACGA  
60 14603 TCCCACACGAGAGCCCATT  
14604 GAGCCCATTTTCAGGTCAA  
14605 TCCAGGTCAAAGCGCTGCA  
14606 AGCGCCTGCAGGAGGAAACG  
14607 GGAGGAAACGGGCCAGGAGA  
65 14608 GGCCAGGAGAGCCGCGACTT  
14609 GCCGCGACTTCTGAGCTCC  
14610 CCTGAGCTCCGGCCGCGGGC  
14611 GGCCGCGGGCTCAGGTCCCT  
14612 TCAGGTCCCTCTCGCGGCAG  
70 14613 CTCGCGGCAGCCCGCGGACT  
14614 CCCGCGGACTTGTCCGGATC  
14615 TGTCCGGATCCGAATAGAG  
14616 CGAATAGAAGCGCTGTTGGA  
14617 CGCTGTTGGATGCGGATGGG  
75 14618 TGCGGATGGGGCGCGGGGT

14619 GCGCCGGGGTTGCCGCCACA  
 14620 TGCCGCCACAGGTGCTTCGG  
 14621 GGTGCTTCGGGGCTCTGGTC  
 5 14622 GGCTCTGGTCATGCTGTGGC  
 14623 ATGCTGTGGCGGCCGCGAGA  
 14624 GGCCGCGAGAGCGACTCAAC  
 14625 GCGACTCAACCTGCTGCAAG  
 14626 CTGCTGCAAGCCTCTGCCCC  
 14627 CCTCTGCCCTTCGCGGACC  
 10 14628 TTCGCCGACCCCCAGTTCT  
 14629 CCCAGGTTCTCCATGCGCCA  
 14630 CCATGCGCCAGAGAAAGGCT  
 14631 GAGAAAGGCTGGATGAAGGG  
 14632 GGATGAAGGGTTCCGACGG  
 15 14633 TTTCCGACGGGTCCCTGCTT  
 14634 GTCCCTGCTTGGCTGCTCCT  
 14635 GGCTGCTCCTAGGCATTGCT  
 14636 AGGCATTGCTGGCGGGCAAG  
 14637 GGCGGCAAGGCCGCCACG  
 20 14638 GGCCGCCACGTTGCTCCGAA  
 14639 TTGCTCCGAACGGTCCGCAG

In one preferred embodiment, the links between neighboring mononucleotides are phosphodiester links. In another preferred, at least one mononucleotide phosphodiester residue of the anti-sense oligonucleotide(s) is substituted by a methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, 2'-O-methyl, methylene(methylimino), methyleneoxy (methylimino), phosphoramidate residues, and combinations thereof. The oligos having one or more phosphodiester residues substituted by one or more of the other residues are generally longer lasting, given that these residues are more resistant to hydrolysis than the phosphodiester residue. In some cases up to about 10%, about 30%, about 50%, about 75%, and even all phosphodiester residues may be substituted (100%).

In another preferred embodiment, the multiple target anti-sense oligo (MTA) of the invention comprises at least about 7 mononucleotides, in some instances up to 60 and more mononucleotides, preferably about 10 to about 36, and more preferably about 12 to about 21 mononucleotides. However, other lengths are also suitable depending on the length of the target macromolecule. Examples of multi-targeted anti-sense (MTA) oligos of the invention are provided in Table 3 below, which includes ninety-four sequences (SEQ ID NOS.: 2316 through 2410).

Table 3: MTA Oligos, Location Targeted &amp; Target

MTA Oligo	SEQ. ID No.	Location	Compound Targeted	Target
<b>HUMNFKBP65A AS</b>				
CCC GGC CCC GCC TCG TGC C	12388	5'=1	EPI 2192	
CGT CCB TGC CGC GGG CCC	12389	5'=28 (AUG)	EPI 2193	
gcc ccg ctg ctt ggg ctg ctc tgc cgg g	12390	5'=65	EPI 2194	
TCT GTG CTC CTC TCG CCT GGG	12391	5'=137	EPI 2195	
45 TGG TGG GGT GGG TCT TGG TGG	12392	5'=159	EPI 2196	
CTG TCC CTG GTC CTG TG	12393	5'=196	EPI 2197	
GGT CCC GCT TCT TC	12394	5'=362	EPI 2198	
GGG GTT GTT GTT GGT CTG G	12395	5'=401	EPI 2199	
TGT CCT CTT TCT GC	12396	5'=656	EPI 2200	
50 GCC TCG GGC CTC CC	12397	5'=697	EPI 2201	
GGC TGG GGT CTG CGT	12398	5'=769	EPI 2202	
GGC CGG GGG TCG GTG GGT CCG CTG	12399	5'=953	EPI 2203	
GGG CTG GGG TGC TGG CTT GGG G	12400	5'=1022	EPI 2204	
GGG GCT GGG GCC TGG GCC	12401	5'=1208	EPI 2205	
55 GCC TGG GTG GGC TTG GGG GC	12402	5'=1272	EPI 2206	
GCT GGG TCT GTG CTG TTG CC	12403	5'=1362	EPI 2207	
GTT GTG TGG GGG GCC	12404	5'=1451	EPI 2208	
GCT GGG TCG GGG GGC CTC TGG GCT GTC	12405	5'=1511	EPI 2209	
GCC CCG GGG CCC CC	12406	5'=1550	EPI 2210	
60 TGG CTC CCC CCT CC	12407	5'=1772	EPI 2211	
GCT CCC CCC TTT CC	12408	5'=1863	EPI 2212	
CGG ACG AAG ACA GAG A	12409	5'=1979	EPI 2213	
GGC TTT GTG GGC TC	12410	5'=2011	EPI 2214	
GCC TGC TCT CCC CC	12411	5'=2312	EPI 2215	
65 CCC GGC CCC GCC BCG BBC C	12412	intron	EPI 2192-01A	HSU50136C4Synth



CCC GGC CCC GCC BCG	12413	intron	EPI 2192-01B	
CCC GGC CCC GCC BCG BBC C	12414	5'untr	EPI 2192-02A	HUMLIPOXSLO
CCC GGC CCC GCC BCG	12415	5'untr	EPI 2192-02B	
CCC GBC CCC GCC TCB BG	12416	trans	EPI 2192-03A	HSNFKBS Subunit
5 CCC GBC CCC GCC TC	12417	trans	EPI 2192-03B	
CCG GCC CCG CCT C	12418	5'untr	EPI 2192-04	TGFβR1
CCC GBB CCC GCB TBG TGC C	12419	5'trans	EPI 2192-05A	HSU58198I1 enhan
CCC GCB TBG TGC C	12420	5'untr	EPI 2192-05B	
CCC GGB CCC BCC BBG TGC C	12421	3'trans	EPI 2192-06	HSVECAD
10 CBG BBC CCG CCT CGT GCC	12422	intron	EPI 2192-07A	NFKB2
C CCG CCT CGT GCC	12423	intron	EPI 2192-07B	NFKB2
CCG GCB CCG CCT CBT GCC	12424	5'trans	EPI 2192-08	Carboxypep
CCG GCC CCG CCB CBT GCC	12425	3'trans	EPI 2192-09	HumADRA2Cα2AdrKid
CCC GBC CCC GBC TCG	12426	5'untrs	EPI 2192-10	HUMPK506B
15 CCC GGC CBC GBC TCG	12427	5'untrs	EPI 2192-11	HSNBARKS1βAdrKin
CCC GGC CCB GCC TBG	12428	5'UTR	EPI 2192-12	HSNFXN1 (NFKB1)
CCC GGC BCB GBC TCG TBC C	12429	3'UTR	EPI 2192-13	HSILF(transcrp. Factor ILF)
20 CCC GGC CCC GCC BCG	12413		EPI-2192-14	NFKB/C4Syn/5-LO/ TGFβrec1 MTA
CCC GGC CCC GCC BCG	12430		EPI-2192-15	NFKB/C4Syn/5-LOMTA
TCC BTG CCG CGG GC	12432	3' trans	EPI-2193-01	METOnco gene
TCC BTG CCB CGG GCC	12433	3' trans	EPI-2193-02	HSFGR2 (IG)
25 TCC BTG CCB CGG GCC	12434	mid cod	EPI-2193-03	5-LO
GTC CBT GBC GCG G	12435	mid cod	EPI-2193-04	HUMTK14
TC CBT GBC GCG GG	12436	3'trans	EPI-2193-05	HUMTNFR
	12437	AUG		Probl.HUMPTCH cardiacK+channel
30 TCT GBG CTC CTC TBB CCT GGG	12438	intr	EPI-2195-01	humCSPAcytotox. Ser. Protease
CTG TGC BCC TBB CBC CTG GG	12439	intr	EPI-2195-02	HSINOSX08induc.NOS
TGT GBT CCB CTB GBC TGG G	12440		EPI-2195-03	HUMACHRM2musc.m2 acetylch.rec.
35 TCT GTB CTC BBC TCB CCT G	12441		EPI-2195-04	s86371s1 Neurokinin3Recept
TGC TCC TCB CBB CTG GG	12442		EPI-2195-05	HUMMIP1 Amacro Inflam. Factor
CTC CTC TBG CCT GG	12443		EPI-2195-06	HSNBARKS4
β-Adr Rec Kinase				
40 GTG CTC CBB TCB BCT GGG	12444		EPI-2195-07	HSTNFR2S06TNF R2
GTG CBC CBB TCB CCT GGG	12445		EPI-2195-08	humfkbp fk506
binding prot.				
TCT GTG CBC CTC TBG BCT	12446	exon	EPI-2195-09	HSNBARKS1β-Adr. Recept. Kinase
45 CTG TBB TCC TBB CBC CTG G	12482	intron	EPI-2195-10	HUMIL8
TGT GCT BBT CBC BCB TGG G	12448		EPI-2195-11	HSU50157 PDE4
GTG CBC CBC TCB CCT G	12449	intron/exon	EPI-2195-12	IL-2 R
CTG TGC BCC TCT C	12450	3'UTR	EPI-2203-05	IL-6 R HSIL6R
CBG TGC BCC BCT CBC CTG	12451	intr/ex	EPI-2203-06A	HSIL2rG6
50 G TGC BCC BCT CBC CTG	12449	intr/ex	EPI-2203-06B	HSIL2rG6
CBC CTC TCB CCT GGG	12453	coding	EPI-2203-07A	HUMIL71
C CTC TCB CCT GGG	12454	coding	EPI-2203-07B	IL-7 HUMIL71
GCT CCB CTC GCC T	12455	coding	EPI-2203-08	IL-6 R HSI6REC
TGC TCC TCB CGC C	12456	intron PDGF A	EPI-2303-09	Chain HUMPDGFAB
55 GTT GTT GBT CTG G	12457	3'utr	EPI-2199-01	GATA-4Transcrip.
Factor for IL-5				
GGT TGB BBT TGG TCT TGG	12458	Coding	EPI-2199-02	TNFα HUMTNFA
GGT TGT TGB TGB TCT G	12459	Far 5'UTR	EPI-2199-03	HSSUBP1G(Sub Pr)
60 GGG TTB BBG TTG BTC TGG	12460	Coding	EPI-2199-04	NeutrophilAdh. R HUMNARIA
GGG TTB BBG TTG BTC TGG	12461	HSBM2	EPI-2199-05	m2 Muscarinic R
TTG TTG TBG BTC TGG	12462	HUML1CAM	EPI-2199-06	L1 LeukAadhProt
GGG TBG BBG BGT CCG CTG	12463	coding	EPI-2203-01	HUMGATA2A
GGG TCB GBG GBT CBG CTG	12464	S71424S2	EPI-2203-02	IGE eps
65 GGG TBG GTG GGT C	12465	coding	EPI-2203-03	HSGCSFR2
GGG TCG GBG GGT CBG C	12466	HUMITGF	EPI-2203-04	TGFβ3
GGG TGG GCT T	12485	HUMNK65PRO	EPI-2206-01	NFKB/NK & TCell
				Activating Prot
70 GGG TGG GCT TGG G	12468	HUMPEREEB	EPI 2206-02	NFKB/Prostagl. EP3 Rec

	CCTGGGTGGGBBTGGG	12469	EPI 2206-03	HSNF2B/GCSF NFKB/GranuLocCSF/ Transcr. FactorNF2B
5	CCTGGBTGGGCBTGGG	12470	EPI-2206-04	HUMLAP/NFKB Leuk. Adhes. Prot
	GCCTGBGTGBBCTTGGG	12471	EPI2206-05	NFKB/Endothel
	N2 S63833			
	CCCAVGVCVCCAGGC	11769	EPI 2206-06	NFKBAS13/B Lymph SerThrProt. Kinase
10	AGCCCACCCAGGC	11770	EPI2206-07	NFKBAS13/GCSF1 HSGCSFR1Rec
	BCCTGGGTGGGCTB	11771	EPI2206-08	NFKBAS13/GCSF1/ NK7TCELLACT. Prot
	GGTGGGCTTGGG	11772	EPI 2206-09	NFKBAS13/
15	HSTGFB1 TGFB	11773	EPI 2206-10	NFKBAS13/ HSTGFB1 TGFB1
	CCBBGGTGGGCTTGGG	11774	EPI 2206-11	NFKBAS13/
	CTGGGTGGGBBTGGG	11775	EPI 2206-12	NFKBAS13/HUMCD30A LymphActAntigCoding
20	HSGCSFR1 GCSFR1	11776	EPI-2206-12B	NFKBAS13/HUMCD30A
	CCBGGGTGGGCTTGG	11777	EPI 2206-13	NFKBAS13/HUMCAM1V Vasc. Endoth. Cell Adh. Molec
25	GGGTGGGCTTGG			
	CCTGBGTGBGCBTGGG			
B: Universal Base				

The MTA oligos of Table 3 and others in accordance with this invention are suitable for use with two or more of the targets, such as those listed in Table 4 below.

30 Table 4: Targets for the MTA Oligos of Table 3

Compound	Target
EPI 2010	Adenosine A1 receptor
EPI 2045	Adenosine A3 receptor
EPI 2873, EPI 2193	NFκB
EPI 1873	Interleukin-1
EPI 1857	Interleukin -5
EPI 2945	Interleukin -4
EPI 2977	Interleukin -8
EPI 2031	5-Lipoxygenase
EPI 1898	Leukotriene C-4 Synthase
EPI 1856	Eotaxin
EPI 1131	ICAM
EPI 1085	VCAM
EPI 2085	TNFα
EPI 1908	PAF
EPI 1925	IL-4 receptor
EPI 2643	β2 adrenergic receptor kinase
EPI 2934	Tryptase
EPI 2033	Major Basic Protein
EPI 2795	Eosinophil Peroxidase

NfκB: nuclear factor κB  
 ICAM: intracellular adhesion molecule  
 VCAM: vascular cell adhesion molecule  
 TNF: tumor necrosis factor  
 PAF: platelet activating factor

The mRNA sequence of the targeted protein or the DNA sequence of the regulatory segment may be derived from the nucleotide sequence of the gene expressing or regulating the protein, whether for existing targets or

those to be found in the future. Sequences for many target genes of different systems are presently known. See, GenBank data base, NIH, the entire sequences of which are incorporated here by reference. The sequences of those genes, whose sequences are not yet available, may be obtained by isolating the target segments applying technology known in the art. Once the sequence of the gene, its RNA and/or the protein are known, anti-sense oligonucleotides are produced as described above and utilized to validate the target by in vivo administration and testing for a reduction of the production of the targeted protein in accordance with standard techniques, and of specific functions.

As already described above, the anti-sense oligonucleotides may be of any suitable length, e.g., from about 7 to about 60 nucleotides in length, depending on the particular target being bound and the mode of delivery thereof. The anti-sense oligonucleotide preferably is directed to an mRNA region containing a junction between intron and exon or to regions vicinal to the junction. Where the anti-sense oligonucleotide is directed to an intron/exon junction, it may either entirely overlie the junction or may be sufficiently close to the junction to inhibit splicing out of the intervening exon during processing of precursor mRNA to mature mRNA, e.g., with the 3' or 5' terminus of the anti-sense oligonucleotide being positioned within about, for example, 10, 5, 3, or 2 nucleotide of the intron/exon junction. Also preferred are anti-sense oligonucleotides which overlap the initiation codon and, more generally, those that target the coding region of the target mRNA. When practicing the present invention, the anti-sense oligonucleotide(s), administered, whether DNA or RNA may be related in origin to the species to which it is administered or to other species including prokaryotes. When treating humans, human anti-sense may be used if desired, except when targeting foreign invaders. Anti-sense oligos to endogenous sequences of other species, however, are also clearly encompassed.

Other agents that may be incorporated into the present composition are one or more of a variety of therapeutic agents which are administered to humans and animals. Some of the categories of agents suitable for incorporation into the present composition and formulations are analgesics, pre-menstrual medications, menopausal agents, anti-aging agents, anti-anxiolytic agents, mood disorder agents, anti-depressants, anti-bipolar mood agents, anti-schizophrenic agents, anti-cancer agents, alkaloids, blood pressure controlling agents, hormones, anti-inflammatory agents, muscle relaxants, soporific agents, anti-ischemic agents, anti-arrhythmic agents, contraceptives, vitamins, minerals, tranquilizers, neurotransmitter regulating agents, wound healing agents, anti-angiogenic agents, cytokines, growth factors, anti-metastatic agents, antacids, anti-histaminic agents, anti-bacterial agents, anti-viral agents, anti-gas agents, appetite suppressants, sun screens, emollients, skin temperature lowering products, radioactive phosphorescent and fluorescent contrast diagnostic and imaging agents, libido altering agents, bile acids, laxatives, anti-diarrheic agents, skin renewal agents, hair growth agents, analgesics, pre-menstrual medications, anti-menopausal agents such as hormones and the like, anti-aging agents, anti-anxiolytic agents, nociceptive agents, mood disorder agents, anti-depressants, anti-bipolar mood agents, anti-schizophrenic agents, anti-cancer agents, alkaloids, blood pressure controlling agents, hormones, anti-inflammatory agents, other agents suitable for the treatment and prophylaxis of diseases and conditions associated or accompanied with pain and inflammation, such as arthritis, burns, wounds, chronic bronchitis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease such as Crohn's disease and ulcerative colitis, autoimmune disease such as lupus erythematosus, muscle relaxants, steroids, soporific agents, anti-ischemic agents, anti-arrhythmic agents, contraceptives, vitamins, minerals, tranquilizers, neurotransmitter regulating agents, wound and burn healing agents, anti-angiogenic agents, cytokines, growth factors, anti-metastatic agents, antacids, anti-histaminic agents, anti-bacterial agents, anti-viral agents, anti-gas agents, agents for reperfusion injury, counteracting appetite suppressants, sun screens, emollients, skin temperature lowering products, radioactive phosphorescent and fluorescent contrast diagnostic and imaging agents, libido altering agents, bile acids, laxatives, anti-diarrheic agents, skin renewal agents, hair growth agents, etc.

Among the hormones suitable for active agents of the invention, are female and male sex hormones such as premarin, progesterone, androsterones and their analogues, thyroxine and glucocorticoids, including Budesonide, Dexamethasone, Flunisolide, Triamcinolone, and others. Among the libido altering agents are Viagra and other NO-level modulating agents, among the analgesics are over-the-counter medications such as ibuprofen, oruda, aleve and acetaminophen and controlled substances such as morphine and codeine, among the anti-depressants are tricyclics, MAO inhibitors and epinephrine,  $\gamma$ -amino butyric acid (GABA), dopamine and serotonin level elevating agents, e.g. Prozac, Amytryptilin, Wellbutrin and Zoloft, among the skin renewal agents are Retin-A, hair growth agents such as Rogaine, among the anti-inflammatory agents are non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, among the soporifics are melatonin and sleep inducing agents such as diazepam, cytoprotective, anti-ischemic and

head injury agents such as enadoline, and many others. Examples of agents in the different groups are provided in the following list. Examples of analgesics are Acetaminophen, Anilerdine, Aspirin, Buprenorphine, Butabital, Butorphanol, Choline Salicylate, Codeine, Dezocine, Diclofenac, Diflunisal, Dihydrocodeine, Elcatonin, Etodolac, Fenoprofen, Hydrocodone, Hydromorphone, Ibuprofen, Ketoprofen, Ketorolac, Levorphanol, Magnesium Salicylate, Meclofenamate, Mefenamic Acid, Meperidine, Methadone, Methotrimeprazine, Morphine, Nalbuphine, Naproxen, Opium, Oxycodone, Oxymorphone, Pentazocine, Phenobarbital, Propoxyphene, Salsalate, Sodium Salicylate, Tramadol and Narcotic analgesics in addition to those listed above. See, Mosby's Physician's GenRx. Examples of anti-anxiety agents include Alprazolam, Bromazepam, Buspirone, Chlordiazepoxide, Chlormezanone, Clorazepate, Diazepam, Halazepam, Hydroxyzine, Ketazolam, Lorazepam, Meprobamate, Oxazepam and Prazepam, among others. Examples of anti-anxiety agents associated with mental depression are Chlordiazepoxide, Amitriptyline, Loxapine, Maprotiline and Perphenazine, among others. Examples of anti-inflammatory agents are non-rheumatic Aspirin, Choline Salicylate, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Floctafenine, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Magnesium Salicylate, Meclofenamate, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Phenylbutazone, Piroxicam, Salsalate, Sodium Salicylate, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolmetin. Examples of anti-inflammatories for ocular treatment are Diclofenac, Flurbiprofen, Indomethacin, Ketorolac, Rimexolone (generally for post-operative treatment). Examples of anti-inflammatories for non-infectious nasal applications are Beclomethaxone, and the like. Examples of soporifics (anti-insomnia/sleep inducing agents) such as those utilized for treatment of insomnia, are Alprazolam, Bromazepam, Diazepam, Diphenhydramine, Doxylamine, Estazolam, Flurazepam, Halazepam, Ketazolam, Lorazepam, Nitrazepam, Prazepam, Quazepam, Temazepam, Triazolam, Zolpidem and Sopiclone, among others. Examples of sedatives are Diphenhydramine, Hydroxyzine, Methotrimeprazine, Promethazine, Propofol, Melatonin, Trimeprazine, and the like. Examples of sedatives and agents used for treatment of petit mal and tremors, among other conditions, are Amitriptyline HCl, Chlordiazepoxide, Amobarbital, Secobarbital, Aprobital, Butabarbital, Ethchlorvynol, Glutethimide, L-Tryptophan, Mephobarbital, Methohexital Na, Midazolam HCl, Oxazepam, Pentobarbital Na, Phenobarbital, Secobarbital Na, Thiamylal Na, and many others. Agents used in the treatment of head trauma (Brain Injury/Ischemia) include Enadoline HCl (e.g. for treatment of severe head injury, orphan status, Warner Lambert). Examples of cytoprotective agents and agents for the treatment of menopause and menopausal symptoms are Ergotamine, Belladonna Alkaloids and Phenobarbitals. Examples of agents for the treatment of menopausal vasomotor symptoms are Clonidine, Conjugated Estrogens and Medroxyprogesterone, Estradiol, Estradiol Cypionate, Estradiol Valerate, Estrogens, conjugated Estrogens, esterified Estrone, Estropipate and Ethinyl Estradiol. Examples of agents for treatment of symptoms of Pre Menstrual Syndrome (PMS) are Progesterone, Progestin, Gonadotrophic Releasing Hormone, oral contraceptives, Danazol, Luprolide Acetate and Vitamin B6. Examples of agents for the treatment of emotional/psychiatric treatments are Tricyclic Antidepressants including Amitriptyline HCl (Elavil), Amitriptyline HCl, Perphenazine (Triavil) and Doxepin HCl (Sinequan). Examples of tranquilizers, anti-depressants and anti-anxiety agents are Diazepam (Valium), Lorazepam (Ativan), Alprazolam (Xanax), SSRI's (selective Serotonin reuptake inhibitors), Fluoxetine HCl (Prozac), Sertaline HCl (Zoloft), Paroxetine HCl (Paxil), Fluvoxamine Maleate (Luvox), Venlafaxine HCl (Effexor), Serotonin, Serotonin Agonists (Fenfluramine), and other over the counter (OTC) medications. Examples of anti-migraine agents are Imitrex and the like.

The amount of each active agent may be adjusted when, and if, additional agents with overlapping activities are included as discussed in this patent. The dosage of the active compounds, however, may vary depending on age, weight, and condition of the subject. Treatment may be initiated with a small dosage, e.g. less than the optimal dose, of the first active agent of the invention, whether an anti-inflammatory steroid or a ubiquinone, or both, and optionally other bioactive agents described above. This may be similarly done with the second active agent, until a desirable level is attained. Or vice versa, for example in the case of multivitamins and/or minerals, the subject may be stabilized at a desired level of these products and then administered the first active compound. The dose may be increased until a desired and/or optimal effect under the circumstances is reached. In general, the active agent is preferably administered at a concentration that will afford effective results without causing any unduly harmful or deleterious side effects, and may be administered either as a single unit dose, or if desired in convenient subunits administered at suitable times throughout the day. The second therapeutic or diagnostic agent(s) is (are) administered in amounts which are known in the art to be effective for the intended application. In cases where the second agent has an overlapping activity with the principal agent, the dose of one of the other or of both agents may

be adjusted to attain a desirable effect without exceeding a dose range which avoids untoward side effects. Thus, for example, when other analgesic and anti-inflammatory agents are added to the composition, they may be added in amounts known in the art for their intended application or in doses somewhat lower than when administered by themselves.

5        Pharmaceutical compositions and kits comprising an anti-sense oligo and/or the non-corticoid steroid and/or ubiquinone including doses effective to reduce expression of target protein(s) by binding specifically with DNA or mRNA either encoding, or regulating the expression of the target proteins in the cell so as to prevent its translation are also part of the present invention. Such compositions are provided in a suitable pharmaceutically or veterinarily acceptable carrier(s), e.g., sterile pyrogen-free saline solution either separately or in combination when  
10        intended for dual administration, e.g. in a kit where both first and second agent are administered on specified dates whereas only one is administered other days. The active agents may be formulated with a hydrophobic carrier capable of passing through a cell membrane, e.g., in a liposome, with the liposomes carried in a pharmaceutically acceptable aqueous carrier. The oligonucleotides may also be coupled to a substance which inactivates mRNA, such as a ribozyme. Such oligonucleotides may be administered to a subject to inhibit the activation of a target, such as  
15        the adenosine receptors, which subject is in need of such treatment for any of the reasons discussed herein. Furthermore, the pharmaceutical formulation may also contain chimeric molecules comprising anti-sense oligonucleotides attached to molecules which are known to be internalized by cells. These oligonucleotide conjugates utilize cellular uptake pathways to increase cellular concentrations of oligonucleotides. Examples of macromolecules used in this manner include transferrin, asialoglycoprotein (bound to oligonucleotides via polylysine) and streptavidin. In the pharmaceutical formulation, the anti-sense compound may be contained within a  
20        lipid particle or vesicle, such as a liposome or microcrystal. The particles may be of any suitable structure, such as unilamellar or plurilamellar, so long as the anti-sense oligonucleotide is contained therein. Positively charged lipids such as N- [1-(2, 3 -dioleoyloxy) propyl] -N, N, N-trimethylammoniummethylsulfate, or "DOTAP," are particularly preferred for such particles and vesicles. The preparation of such lipid particles is well known. See, e.g., U.S. Patent  
25        Nos. 4,880,635 to Janoff et al.; 4,906,477 to Kurono et al.; 4,911,928 to Wallach; 4,917,951 to Wallach; 4,920,016 to Allen et al.; 4,921,757 to Wheatley et al.; etc.

The active compounds provided in this patent are preferably administered to the subject as a pharmaceutical or veterinary composition. Pharmaceutical compositions for use in the present invention include formulations suitable for systemic and topical administration, including by inhalation, intrapulmonary infusion,  
30        nasal, respirable, oral, topical (including buccal, sublingual, dermal and intraocular), parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal, vaginal, ophthalmic, otical, implantable, and transdermal and iontophoretic administration, among others. The compositions may conveniently be provided in bulk, or presented in unit or multiple unit dosage form, and may be prepared by any of the methods well known in the art.

35        The first and second active compounds may be administered to the lungs, i.e. intrapulmonarily, nasally, respirably or by inhalation, of a subject by any suitable means. A preferred method of administration is by generating an aerosol or spray comprised of nasal or respirable particles comprising the active compound. The thus administered particles are then inhaled by the subject, i.e. by inhalation, intrapulmonary drip, or nasal administration, or by direct administration into the airways or respiration. The respirable particles may be liquid or  
40        solid, and they are preferably in the range of about 0.05, about 0.5, about 1, about 2, about 2.5 to about 3.5, about 4, about 6, about 8, about 10 micron, and preferably about 1 to about 5 micron (respirable or inhalable particles), or about 10, about 15, about 20, about 30 to about 50, about 100, about 150, about 200, about 300, about 400, about 500 micron, preferably about 10 to about 50, about 100 micron for intrapulmonary instillation or nasal administration. As explained above, particles of non-respirable size that are included in the aerosol or spray tend to  
45        deposit in the throat and be swallowed, and the quantity of non-respirable particles in the aerosol is preferably minimized. For nasal administration or intrapulmonary instillation, particularly for newborn babies and infants, a particle size in the range of about 10 to about 50 microns is preferred to ensure deposition and retention in the nasal or pulmonary cavity. Liquid pharmaceutical compositions of the active compound for producing an aerosol or spray may be prepared by combining the active compound with a stable vehicle, such as sterile pyrogen free water. Solid  
50        particulate compositions containing respirable dry particles of micronized active compound may be prepared by grinding dry active compound with a mortar and pestle, and then passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates. Another method would include passing through a mill

and collecting the fine particles from the device for further classification. A solid particulate composition comprised of the active compound may optionally contain a dispersant that serves to facilitate the formation of an aerosol. A suitable dispersant is lactose, which may be blended with the active compound in any suitable ratio, e. g. a 1 to 2.5 ratio by weight. Again, other therapeutic and formulation compounds may also be included, such as a surfactant to improve the state of surfactant in the lung and help with the absorption of the active agent.

The dosage of the anti-sense compound administered will depend upon the disease being treated, the condition of the subject, the particular formulation, the route of administration, the timing of administration to a subject, etc. In general, intracellular concentrations of the oligonucleotide of from about 0.01, about 0.05, about 0.1, about 0.2, about 1 to about 5  $\mu\text{M}$ , about 50  $\mu\text{M}$ , about 100  $\mu\text{M}$  or more, and more particularly about 0.2 to about 0.5  $\mu\text{M}$ , are desired. For administration to a subject such as a human, a dosage of from about 0.01, about 0.1 or about 1 mg/Kg up to about 50, about 100, or about 150 mg/Kg and even higher doses are typically employed depending on the route of administration as is known in the art. Depending on the solubility of the particular formulation of active compound administered, the daily dose may be divided among one or several unit dose administrations. Administration of the anti-sense compounds may be carried out therapeutically (i.e., as a rescue treatment) or prophylactically. Aerosols of liquid particles comprising the active compound may be produced by any suitable means, such as with a nebulizer. See, e. g. U.S. Patent No. 4,501,729. Nebulizers are commercially available devices that transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable compositions for use in nebulizer comprise the active ingredient in a liquid carrier or diluent, the active ingredient comprising about 0.05 up to about 40% w/w of the composition, preferably about 1 to less than about 20% w/w. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example sodium chloride. Other carriers, however, are also suitable as an artisan would know. Optional additives include preservatives if the composition is not prepared sterile. An example of a preservative is methyl hydroxybenzoate, and other agents such as antioxidants, flavoring agents, volatile oils, buffering agents and surfactants, however, may also be added.

In one preferred embodiment, the pharmaceutical composition may further comprise one or more bronchodilating agents, and one or more surfactants along with a carrier and formulation agents alternatively, these active agents may be administered separately. Suitable surfactants or surfactant components for enhancing the uptake of the anti-sense oligonucleotides of the invention include synthetic and natural as well as full and truncated forms of surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant Protein E, partially and fully saturated phosphatidylcholine (other than dipalmitoyl), dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine; phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholine, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate; as well as natural and artificial lamellar bodies which are the natural carrier vehicles for the components of surfactant, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitinic acid, non-ionic block copolymers of ethylene or propylene oxides, polyoxypropylene, monomeric and polymeric, polyoxyethylene, monomeric and polymeric, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100 and synthetic surfactants ALEC, Exosurf, Survan and Atovaquone, among others. These surfactants may be used either as a single, or as part of a multiple component, surfactant in a formulation, or as covalently bound additions to the 5' and/or 3' ends of the anti-sense oligo(s). Aerosols of solid particles comprising the active compound may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder (e.g., a metered dose thereof effective to carry out the treatments described herein) is contained in capsules or cartridges, typically made of gelatin or foil, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder

blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from about 0.1 to about 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquefied propellant. During the use these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from about 10:1 to about 150:1, to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents. The aerosol, whether formed from solid or liquid particles, may be produced by the aerosol generator for example at a rate of from about 10, about 30, about 70 to about 100, about 150, about 150 liters per minute, more preferably from about 30 to 150 liters per minute, and most preferably about 60 liters per minute. Aerosols containing greater amounts of medicament, however, may be administered more rapidly as is known in the art.

Aerosols of solid particles comprising the active compound may likewise be produced with any solid particulate medicament aerosol generator. Aerosol and spray generators for administering solid particulate medicaments to a subject, comprise product particles that are respirable or inhalable, and they generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration. Examples of such aerosol and spray generators include metered dose inhalers and insufflators known in the art. Liquid pharmaceutical compositions of active compound for producing an aerosol can be prepared by combining the anti-sense compound with the anti-inflammatory steroid(s) and/or the ubiquinone(s) and a suitable vehicle, such as sterile pyrogen free water. Other therapeutic compounds and formulation components may optionally be included as well. Solid particulate compositions containing respirable dry particles of micronized anti-sense compound may be prepared as known in the art, and generally described above, and then passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates.

Compositions suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a pre-determined amount of the first and second active compounds; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such compositions may be prepared by any suitable method of pharmacy that includes the step of bringing into association the active compounds and a suitable carrier. In general, the compositions of the invention are prepared by uniformly and intimately admixing the active compounds with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, tablet may be prepared by compressing or molding a powder or granules containing the active compound(s) alone, or optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s) or surfactants. Molded tablets may be made by molding, in a suitable machine, the powdered compound(s) moistened with an inert liquid binder. Compositions for oral administration may optionally include enteric coatings known in the art to prevent degradation of the compositions in the stomach and provide release of the drug in the small intestine.

Compositions suitable for buccal or sub-lingual administration include lozenges comprising the active compound in a flavored base, usually sucrose and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Compositions suitable for parenteral administration comprise sterile aqueous and non-aqueous injection solutions, suspensions or emulsions of the active compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations may contain anti-oxidants, buffers, surfactants, bacteriostats, solutes which render the compositions isotonic with the blood of the intended recipient, and other formulation components known in the art. Aqueous and non-aqueous sterile suspensions may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or water-for-injection immediately prior to use. Extemporaneous injection solutions, suspensions and emulsions may be prepared from sterile powders, granules and tablets of the kind previously described.



Compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil, although others are also suitable. Carriers that may be used include vaseline, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

Compositions suitable for rectal and vaginal administration are also included and may be prepared by methods known in the art.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Compositions suitable for transdermal administration may also be delivered by iontophoresis. See, e.g. *Pharmaceutical Research* 3:318 (1986). They typically take the form of an optionally buffered aqueous solution of the active compound containing appropriate ions to facilitate the iontophoretic delivery of the agent.

The relevant disclosures of all scientific publications and patent references cited in this patent are specifically intended to be incorporated herein by reference, particularly in reference to preparatory methods and technologies which are enabling of the invention. The following examples are provided to illustrate the present invention, and should not be construed as limiting thereon.

### EXAMPLES

In the following examples,  $\mu$ M means micromolar, ml means milliliters,  $\mu$ m means micrometers, mm means millimeters, cm means centimeters, EC means degrees Celsius,  $\mu$ g means micrograms, mg means milligrams, g means grams, kg means kilograms, M means molar, and h or hr. means hours.

#### Example 1: Design and Synthesis of Anti-sense Oligonucleotides

The design of anti-sense oligonucleotides against the  $A_1$  and  $A_3$  adenosine receptors may require the solution of the complex secondary structure of the target  $A_1$  receptor mRNA and the target  $A_3$  receptor mRNA. After generating this structure, anti-sense nucleotide are designed which target regions of mRNA which might be construed to confer functional activity or stability to the mRNA and which optimally may overlap the initiation codon. Other target sites are readily usable. As a demonstration of specificity of the anti-sense effect, other oligonucleotides not totally complementary to the target mRNA, but containing identical nucleotide compositions on a w/w basis, are included as controls in anti-sense experiments.

The mRNA secondary structure of the adenosine  $A_1$  receptor was analyzed and used as described above. to design a phosphorothioate anti-sense oligonucleotide. The anti-sense oligonucleotide which was synthesized was designated HAdA<sub>1</sub>AS and had the following sequence: 5' -GAT GGA GGG CGG CAT GGC GGG-3' (SEQ ID NO:9370). As a control, a mismatched phosphorothioate anti-sense nucleotide designated HAdA1MM1 was synthesized with the following sequence: 5' -GTA GCA GGC GGG GAT GGG GGC-3' (SEQ ID NO:9371). Each oligonucleotide had identical base content and general sequence structure. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligonucleotide was specific for the human and rabbit adenosine  $A_1$  receptor genes, and that the mismatched control was not a candidate for hybridization with any known gene sequence.

The secondary structure of the adenosine  $A_3$  receptor mRNA was similarly analyzed and used as described above to design two phosphorothioate anti-sense oligonucleotides. The first anti-sense oligonucleotide (HAdA3AS1) synthesized had the following sequence: 5' -GTT GTT GGG CAT CTT GCC-3' (SEQ ID NO:9372). As a control, a mismatched phosphorothioate anti-sense oligonucleotide (HAdA3MM1) was synthesized, having the following sequence: 5' -GTA CTT GCG GAT CTA GGC-3' (SEQ ID NO:9373). A second phosphorothioate anti-sense oligonucleotide (HAdA3AS2) was also designed and synthesized, having the following sequence: 5' -GTG GGC CTA GCT CTC GCC-3' (SEQ ID NO:9374). Its control oligonucleotide (HAdA3MM2) had the sequence: 5' -GTC GGG GTA CCT GTC GGC-3' (SEQ ID NO:9375). Phosphorothioate oligonucleotides were synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, MD).

#### Example 2: In Vivo Testing of Adenosine $A_1$ Receptor Anti-sense Oligos

The anti-sense oligonucleotide against the human  $A_1$  receptor (SEQ ID NO:9370) described above. was tested for efficacy in an in vitro model utilizing lung adenocarcinoma cells HTB-54. HTB-54 lung adenocarcinoma cells were demonstrated to express the  $A_1$  adenosine receptor using standard northern blotting procedures and

receptor probes designed and synthesized in the laboratory.

HTB-54 human lung adenocarcinoma cells (106/100 mm tissue culture dish) were exposed to 5.0 :M HAdA1AS or HAdA1MM1 for 24 hours, with a fresh change of media and oligonucleotides after 12 hours of incubation. Following 24 hour exposure to the oligonucleotides, cells were harvested and their RNA extracted by standard procedures. A 21-mer probe corresponding to the region of mRNA targeted by the anti-sense (and therefore having the same sequence as the anti-sense, but not phosphorothioated) was synthesized and used to probe northern blots of RNA prepared from HAdA1AS-treated, HAdA1MM1-treated and non-treated HTB-54 cells. These blots showed clearly that HAdA1AS but not HAdA1MM1 effectively reduced human adenosine receptor mRNA by >50%. This result showed that HAdA1AS is a good candidate for an anti-asthma drug since it depletes intracellular mRNA for the adenosine A<sub>1</sub> receptor, which is involved in asthma.

**Example 3: In Vivo Efficacy of Adenosine A<sub>1</sub> Receptor Anti-sense Oligos**

A fortuitous homology between the rabbit and human DNA sequences within the adenosine A<sub>1</sub> gene overlapping the initiation codon permitted the use of the phosphorothioate anti-sense oligonucleotides initially designed for use against the human adenosine A<sub>1</sub> receptor in a rabbit model. Neonatal New Zealand white Pasteurella-free rabbits were immunized intraperitoneally within 24 hours of birth with 312 antigen units/ml house dust mite (*D. farinae*) extract (Berkeley Biologicals, Berkeley, CA), mixed with 10% kaolin. Immunizations were repeated weekly for the first month and then biweekly for the next 2 months. At 3-4 months of age, eight sensitized rabbits were anesthetized and relaxed with a mixture of ketamine hydrochloride (44 mg/kg) and acepromazine maleate (0.4 mg/kg) administered intramuscularly. The rabbits were then laid supine in a comfortable position on a small molded, padded animal board and intubated with a 4.0-mm intratracheal tube (Mallinkrodt, Inc., Glens Falls, NY). A polyethylene catheter of external diameter 2.4 mm with an attached latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiments. The intratracheal tube was attached to a heated Fleisch pneumotachograph (size 00; DOM Medical, Richmond, VA), and flow was measured using a Validyne differential pressure transducer (Model DP-45161927; Validyne Engineering Corp., Northridge, CA) driven by a Gould carrier amplifier (Model 11-4113; Gould Electronic, Cleveland, OH). The esophageal balloon was attached to one side of the differential pressure transducer, and the outflow of the intratracheal tube was connected to the opposite side of the pressure transducer to allow recording of transpulmonary pressure. Flow was integrated to give a continuous tidal volume, and measurements of total lung resistance (RL) and dynamic compliance (C<sub>dyn</sub>) were calculated at isovolumetric and flow zero points, respectively, using an automated respiratory analyzer (Model 6; Buxco, Sharon, CT). Animals were randomized and on Day 1 pretreatment values for PC<sub>50</sub> were obtained for aerosolized adenosine. Anti-sense (HAdA1AS) or mismatched control (HAdA1MM) oligonucleotides were dissolved in sterile physiological saline at a concentration of 5000 µg (5 mg) per 1.0 ml. Animals were subsequently administered the aerosolized anti-sense or mismatch oligonucleotide via the intratracheal tube (approximately 5000 :g in a volume of 1.0 ml), twice daily for two days. Aerosols of either saline, adenosine, or anti-sense or mismatch oligonucleotides were generated by an ultrasonic nebulizer (DeVilbiss, Somerset, PA), producing aerosol droplets 80% of which were smaller than 5 :m in diameter. In the first arm of the experiment, four randomly selected allergic rabbits were administered anti-sense oligonucleotide and four the mismatched control oligonucleotide. On the morning of the third day, PC<sub>50</sub> values (the concentration of aerosolized adenosine in mg/ml required to reduce the dynamic compliance of the bronchial airway 50% from the baseline value) were obtained and compared to PC<sub>50</sub> values obtained for these animals prior to exposure to oligonucleotide. Following a 1 week interval, animals were crossed over, with those previously administered mismatch control oligonucleotide now administered anti-sense oligonucleotide, and those previously treated with anti-sense oligonucleotide now administered mismatch control oligonucleotide. Treatment methods and measurements were identical to those employed in the first arm of the experiment. It should be noted that in six of the eight animals treated with anti-sense oligonucleotide, adenosine-mediated bronchoconstriction could not be obtained up to the limit of solubility of adenosine, 20 mg/ml. For the purpose of calculation, PC<sub>50</sub> values for these animals were set at 20 mg/ml. The values given therefore represent a minimum figure for anti-sense effectiveness. Actual effectiveness was higher. The results of this experiment are illustrated in Table 5 below.

**Table 5:** Effect of Adenosine A<sub>1</sub> Receptor Anti-sense Oligo upon PC<sub>50</sub> Values in Asthmatic Rabbits

Mismatch Control		A <sub>1</sub> Receptor Anti-sense Oligo	
Pre Oligonucleotide	Post Oligonucleotide	Pre Oligonucleotide	Post Oligonucleotide
3.56 ± 1.02	5.16 ± 1.03	2.36 ± 0.68	>19.5 ± 0.34**

The results are presented as the mean (n=8) ± SEM.

The significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected test.

\*\*Significantly different from all other groups, p<0.01.

In both arms of the experiment, animals receiving the anti-sense oligonucleotide showed an order of magnitude increase in the dose of aerosolized adenosine required to reduce dynamic compliance of the lung by 50%. No effect of the mismatched control oligonucleotide upon PC<sub>50</sub> values was observed. No toxicity was observed in any animal receiving either anti-sense or control inhaled oligonucleotide. These results show clearly that the lung has exceptional potential as a target for anti-sense oligonucleotide-based therapeutic intervention in lung disease. They further show, in a model system which closely resembles human asthma, that downregulation of the adenosine A<sub>1</sub> receptor largely eliminates adenosine-mediated bronchoconstriction in asthmatic airways. Bronchial hyperresponsiveness in the allergic rabbit model of human asthma is an excellent endpoint for anti-sense intervention since the tissues involved in this response lie near to the point of contact with aerosolized oligonucleotides, and the model closely simulates an important human disease.

**Example 4: Specificity of A<sub>1</sub>-adenosine Receptor Anti-sense Oligonucleotide**

At the conclusion of the cross-over experiment of Example 3 above, airway smooth muscle from all rabbits was quantitatively analyzed for adenosine A<sub>1</sub> receptor number. As a control for the specificity of the anti-sense oligonucleotide, adenosine A<sub>2</sub> receptors, which should not have been affected, were also quantified. Airway smooth muscle tissue was dissected from each rabbit and a membrane fraction prepared according to the method of Kleinstein et al. (Kleinstein, J. and Glossmann, H., Naunyn-Schmiedeberg's Arch. Pharmacol. 305: 191-200 (1978)), the relevant portion of which is hereby incorporated in its entirety by reference, with slight modifications. Crude plasma membrane preparations were stored at -70EC until the time of assay. Protein content was determined by the method of Bradford (M. Bradford, Anal. Biochem. 72, 240-254 (1976), the relevant portion of which is hereby incorporated in its entirety by reference). Frozen plasma membranes were thawed at room temperature and were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37EC to remove endogenous adenosine. The binding of [<sup>3</sup>H] DPCPX (A<sub>1</sub> receptor-specific) or [<sup>3</sup>H] CGS-21680 (A<sub>1</sub> receptor-specific) was measured as previously described by Ali et al. (Ali, S. et al., J. Pharmacol. Exp. Ther. 268, Am. J. Physiol 266, L271-277 (1994), the relevant portion of which is hereby incorporated in its entirety by reference). The animals treated with adenosine A<sub>1</sub> anti-sense oligonucleotide in the cross-over experiment had a nearly 75% decrease in A<sub>1</sub> receptor number compared to controls, as assayed by specific binding of the A<sub>1</sub>-specific antagonist DPCPX. There was no change in adenosine A<sub>2</sub> receptor number, as assayed by specific binding of the A<sub>2</sub> receptor-specific agonist 2- [p- (2-carboxyethyl)-phenethylamino] -5' - (N-ethylcarboxamido) adenosine (CGS-21680). This is illustrated in Table 6 below.

**Table 6:** Specificity of Action of Adenosine A<sub>1</sub> Receptor Oligonucleotide Anti-sense

Mismatch Control Oligonucleotide	A <sub>1</sub> Anti-sense Oligonucleotide	
A <sub>1</sub> -Specific Binding	1105 ± 48**	293 ± 18
A <sub>2</sub> -Specific Binding	302 ± 22	442 ± 171

The results are presented as the mean (n = 8) ± SEM.

The significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected test.

\*\*Significantly different from mismatch control, p<0.01.

The above results illustrate the effectiveness of anti-sense oligonucleotides in treating airway disease. Since the anti-sense oligos described above, eliminate the receptor systems responsible for adenosine-mediated bronchoconstriction, it may be less imperative to eliminate adenosine from them. However, it would be preferable to eliminate adenosine from even these oligonucleotides to reduce the dose needed to attain a similar effect. Described

above are other anti-sense oligonucleotides targeting mRNA of proteins involved in inflammation. Adenosine has been eliminated from their nucleotide content to prevent its liberation during degradation.

**Example 5: Anti-sense Oligos directed to other Target Nucleic Acids**

This work was conducted to demonstrate that the present invention is broadly applicable to anti-sense oligonucleotides ("oligos") specific to nucleic acid targets broadly. The following experimental studies were conducted to show that the method of the invention is broadly suitable for use with anti-sense oligos designed as taught by this application and targeted to any and all adenosine receptor mRNAs. For this purpose, various anti-sense oligos were prepared to adenosine receptor mRNAs exemplified by the adenosine A<sub>1</sub>, A<sub>2b</sub> and A<sub>3</sub> receptor mRNAs. Anti-sense Oligo I was disclosed above (SEQ ID NO:9370). Five additional anti-sense phosphorothioate oligos were designed and synthesized as indicated above.

- 1- Oligo II (SEQ ID NO: 9376) also targeted to the adenosine A<sub>1</sub> receptor, but to a different region than Oligo I.
- 2- Oligo V (SEQ ID NO: 9379) targeted to the adenosine A<sub>2b</sub> receptor.
- 3- Oligos III (SEQ ID NO: 9377) and IV (SEQ ID NO: 9378) targeted to different regions of the adenosine A<sub>3</sub> receptor.
- 4- Oligo I-PD (SEQ ID NO: 11050) (a phosphodiester oligo of the same sequence as Oligo I).

These anti-sense oligos were designed for therapy on a selected species as described above and are generally specific for that species, unless the segment of the target mRNA of other species happens to contain a similar sequences. All anti-sense oligos were prepared as described below, and tested in vivo in a rabbit model for bronchoconstriction, inflammation and allergy, which have breathing difficulties and impeded lung airways, as is the case in ailments such as asthma, as described in the above-identified application.

**Example 6: Design & Sequences of other Anti-sense Oligos**

Six oligos and their effects in a rabbit model were studied and the results of these studies are reported and discussed below. Five of these oligos were selected for this study to complement the data on Oligo I (SEQ ID NO: 9370) provided in Examples 1 to 4 above. This oligo is anti-sense to one region of the adenosine A<sub>1</sub> receptor mRNA. The oligos tested are identified as anti-sense Oligos I (SEQ ID NO: 9370) and II (SEQ ID NO: 9376) targeted to a different region of the adenosine A<sub>1</sub> receptor mRNA, Oligo V (SEQ ID NO:9377) targeted to the adenosine A<sub>2b</sub> receptor mRNA, and anti-sense Oligos III and IV (SEQ ID NOS: 9378 and 9379) targeted to two different regions of the adenosine A<sub>3</sub> receptor mRNA. The sixth oligo (Oligo I-PD) is a phosphodiester version of Oligo I (SEQ ID NO:9370). The design and synthesis of these anti-sense oligos was performed in accordance with Example 1 above.

**(I) Anti-sense Oligo I**

The anti-sense oligonucleotide I referred to in Examples 1 to 4 above is targeted to the human A<sub>1</sub> adenosine receptor mRNA (EPI 2010). Anti-sense oligo I is 21 nucleotide long, overlaps the initiation codon, and has the following sequence: 5'-GAT GGA GGG CGG CAT GGC GGG-3' (SEQ ID NO:9370). The oligo I was previously shown to abrogate the adenosine-induced bronchoconstriction in allergic rabbits, and to reduce allergen-induced airway obstruction and bronchial hyperresponsiveness (BHR), as discussed above and shown by Nyce, J. W. & Metzger, W. J., Nature, 385:721 (1977), the relevant portions of which reference are incorporated in their entireties herein by reference.

**(II) Anti-sense Oligo II**

A phosphorothioate anti-sense oligo (SEQ ID NO:9376) was designed in accordance with the invention to target the rabbit adenosine A<sub>1</sub> receptor mRNA region +936 to +956 relative to the initiation codon (start site). The anti-sense oligo II is 21 nucleotide long, and has the following sequence: 5'-CTC GTC GCC GTC GCC GGC GGG-3' (SEQ ID NO:9376).

**(III) Anti-sense Oligo III**

A phosphorothioate anti-sense oligo other than that provided in Example 1 above (SEQ ID NO:9377) was designed in accordance with the invention to target the anti-sense A<sub>3</sub> receptor mRNA region +3 to +22 relative to the initiation codon start site. The anti-sense oligo III is 20 nucleotide long, and has the following sequence: 5'-GGG TGG TGC TAT TGT CGG GC-3' (SEQ ID NO:9377).

**(IV) Anti-sense Oligo IV**

Yet another phosphorothioate anti-sense oligo (SEQ ID NO:9378) was designed in accordance with the invention to target the adenosine A<sub>3</sub> receptor mRNA region +386 to +401 relative to the initiation codon (start site). The anti-sense oligo IV is 15 nucleotide long, and has the following sequence: 5'-GGC CCA GGC CCA

**GCC-3' (SEQ ID NO:9378)****(V) Anti-sense Oligo V**

A phosphorothioate anti-sense oligo (SEQ ID NO:9379) was designed in accordance with the invention to target the adenosine A<sub>2b</sub> receptor mRNA region -21 to -1 relative to the initiation codon (start site). The anti-sense oligonucleotide V is 21 nucleotide long, and has the following sequence: 5'-GGC CGG GCC AGC CGG GCC CGG-3' (SEQ ID NO:9379).

**(VI) A<sub>1</sub> Mismatch Oligos**

Two different mismatched oligonucleotides having the following sequences were used as controls for anti-sense oligo I (SEQ ID NO: 1) described in Example 5 above: A<sub>1</sub> MM2:5'-GTA GGT GGC GGG CAA GGC GGG-3' (SEQ ID NO:12490), and A<sub>1</sub> MM3:5'-GAT GGA GGC GGG CAT GGC GGG-3' (SEQ ID NO:12489). Anti-sense oligo I and the two mismatch anti-sense oligos had identical base content and general sequence structure. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligo I was specific, not only for the human, but also for the rabbit, adenosine A<sub>1</sub> receptor genes, and that the mismatched controls were not candidates for hybridization with any known human or animal gene sequence.

**(VII) Anti-sense Oligo A<sub>1</sub>-PD (Oligo VI)**

A phosphodiester anti-sense oligo (Oligo VI; SEQ ID NO:9370) having the same nucleotide sequence as Oligo I was designed as disclosed in the above-identified application. Anti-sense oligo I-PD is 21 nucleotide long, overlaps the initiation codon, and has the following sequence: 5'- GAT GGA GGC CGG CAT GGC GGG-3' (SEQ ID NO:9370).

**(III) Controls**

Each rabbit was administered 5.0 ml aerosolized sterile saline following the same schedule as for the anti-sense oligos in (II), (III), and (IV) above.

**Example 7: Synthesis of Anti-sense Oligos**

Phosphorothioate anti-sense oligos having the sequences described in (a) above, were synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, DE). TETD (tetraethylthiuram disulfide) was used as the sulfurizing agent during the synthesis. Anti-sense oligonucleotide II (SEQ ID NO:9376), anti-sense oligonucleotide III (SEQ ID NO: 9377) and anti-sense oligonucleotide IV (SEQ ID NO: 9378) were each synthesized and purified in this manner.

**Example 8: Preparation of Allergic Rabbits**

Neonatal New Zealand white Pasturella-free rabbits were immunized intraperitoneally within 24 hours of birth with 0.5 ml of 312 antigen units/ml house dust mite (*D. farinae*) extract (Berkeley Biologicals, Berkeley, CA) mixed with 10% kaolin as previously described (Metzger, W. J., in Late Phase Allergic Reactions, Dorsch, W., Ed., CRC Handbook, pp. 347-362, CRC Press, Boca Raton (1990); Ali, S., Metzger, W. J. and Mustafa, S. J., Am. J. Resp. Crit. Care Med. 149: 908 (1994)), the relevant portions of which are incorporated in their entirety here by reference. Immunizations were repeated weekly for the first month and then biweekly until the age of 4 months. These rabbits preferentially produce allergen-specific IgE antibody, typically respond to aeroallergen challenge with both an early and late-phase asthmatic response, and show bronchial hyper responsiveness (BHR). Monthly intraperitoneal administration of allergen (312 units dust mite allergen, as above) continues to stimulate and maintain allergen-specific IgE antibody and BHR. At 4 months of age, sensitized rabbits were prepared for aerosol administration as described by Ali et al. (Ali, S., Metzger, W. J. and Mustafa, S. J., Am. J. Resp. Crit. Care Med. 149 (1994)), the relevant section being incorporated in its entirety here by reference.

**DOSE-RESPONSE STUDIES****Example 9: Experimental Setup**

Aerosols of either adenosine (0-20 mg/ml), or anti-sense or one of two mismatch oligonucleotides (5 mg/ml) were separately prepared with an ultrasonic nebulizer (Model 646, DeVilbiss, Somerset, PA), which produced aerosol droplets, 80% of which were smaller than 5 μm in diameter. Equal volumes of the aerosols were administered directly to the lungs via an intratracheal tube. The animals were randomized, and administered aerosolized adenosine. Day 1 pre-treatment values for sensitivity to adenosine were calculated as the dose of adenosine causing a 50% loss of compliance (PC<sub>50</sub> Adenosine). The animals were then administered either the aerosolized anti-sense or one of the mismatch anti-sense oligos via the intratracheal tube (5 mg/1.0 ml), for 2 minutes, twice daily for 2

days (total dose, 20 mg). Post-treatment PC<sub>50</sub> values were recorded (post-treatment challenge) on the morning of the third day. The results of these studies are provided in Example 21 below.

#### **Example 10: Crossover Experiments**

For some experiments utilizing anti-sense oligo I (SEQ ID NO: 9370) and a corresponding mismatch control oligonucleotide A1MM2, following a 2 week interval, the animals were crossed over, with those previously administered the mismatch control A1MM2, now receiving the anti-sense oligo I, and those previously treated with the anti-sense oligo I, now receiving the mismatch control A1MM2 oligo. The number of animals per group was as follows. For mismatch A1MM2 (Control 1), n=7, since one animal was lost in the second control arm of the experiment due to technical difficulties, for mismatch A1MM3 n=4 (Control 2) and for A1AS anti-sense oligo I, n=8. The A1MM3 oligo-treated animals were analyzed separately and were not part of the cross-over experiment. The treatment methods and measurements employed following the cross-over were identical to those employed in the first arm of the experiment. In 6 of the 8 animals treated with the anti-sense oligo I (SEQ ID NO: 9370), no PC<sub>50</sub> value could be obtained for adenosine doses of up to 20 mg/ml, which is the limit of solubility of adenosine. Accordingly, the PC<sub>50</sub> values for these animals were assumed to be 20 mg/ml for calculation purposes. The values given, therefore, represent a minimum figure for the effectiveness of the anti-sense oligonucleotides of the invention. Other groups of allergic rabbits (n=4 for each group) were administered 0.5 or 0.05 mg doses of the anti-sense oligo I (SEQ ID NO: 9370), or the A1MM2 oligo in the manner and according to the schedule described above (the total doses being 2.0 or 0.2 mg). The results of these studies are provided in Example 22 below.

#### **Example 11: Anti-sense Oligo Formulation**

Each one of anti-sense oligos were separately solubilized in an aqueous solution and administered as described for anti-sense oligo I (SEQ ID NO: 9370) in (e) above, in four 5 mg aliquots (20 mg total dose) by means of a nebulizer via endotracheal tube, as described above. The results obtained for anti-sense oligo I and its mismatch controls confirmed that the mismatch controls are equivalent to saline, as described in Example 19 below and in Table 1 of Nyce & Metzger, Nature 385: 721-725 (1997). Because of this finding, saline was used as a control for pulmonary function studies employing anti-sense oligos II, III and IV (SEQ ID NO: 9376, 9377 and 9378).

#### **Example 12: Specificity of Oligo I for Adenosine A<sub>1</sub> Receptor (Receptor Binding Studies)**

Tissue from airway smooth muscle was dissected to primary, secondary and tertiary bronchi from rabbits which had been administered 20 mg oligo I (SEQ ID NO: 9370) in 4 divided doses over a period of 48 hours as described above. A membrane fraction was prepared according to the method of Ali et al. (Ali, S., et al., Am. J. Resp. Crit. Care Med. 149: 908 (1994), the relevant section relating to the preparation of the membrane fraction is incorporated in its entirety hereby by reference). The protein content was determined by the method of Bradford and plasma membranes were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37EC to remove endogenous adenosine. See, Bradford, M. M. Anal. Biochem. 72, 240-254 (1976), the relevant portion of which is hereby incorporated in its entirety by reference. The binding of [<sup>3</sup>H]DPCPX, [<sup>3</sup>H]NPC17731, or [<sup>3</sup>H]CGS-21680 was measured as described by Jarvis et al. See, Jarvis, M.F., et al., Pharmacol. Exptl. Ther. 251, 888-893 (1989), the relevant portion of which is fully incorporated herein by reference. The results of this study are shown in Table 8 and discussed in Example 20 below.

#### **Example 13: Pulmonary Function Measurements (Compliance c<sub>DYN</sub> and Resistance)**

At 4 months of age, the immunized animals were anesthetized and relaxed with 1.5 ml of a mixture of ketamine HCl (35 mg/kg) and acepromazine maleate (1.5 mg/kg) administered intramuscularly. After induction of anesthesia, allergic rabbits were comfortably positioned supine on a soft molded animal board. Salve was applied to the eyes to prevent drying, and they were closed. The animals were then intubated with a 4.0 mm intermediate high-low cuffed Murphy 1 endotracheal tube (Mallinckrodt, Glen Falls, NY), as previously described by Zavala and Rhodes. See, Zavala and Rhodes, Proc. Soc. Exp. Biol. Med. 144: 509-512 (1973), the relevant portion of which is incorporated herein by reference in its entirety. A polyethylene catheter of OD 2.4 mm (Becton Dickinson, Clay Adams, Parsippany NJ) with an attached thin-walled latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiment. The endotracheal tube was attached to a heated Fleisch pneumotach (size 00; DEM Medical, Richmond, VA), and the flow (v) measured using

a Validyne differential pressure transducer (Model DP-45-16-1927, Validyne Engineering, Northridge, CA), driven by a Gould carrier amplifier (Model 11-4113, Gould Electronics, Cleveland, OH). An esophageal balloon was attached to one side of the Validyne differential pressure transducer, and the other side was attached to the outflow of the endotracheal tube to obtain transpulmonary pressure ( $P_{tp}$ ). The flow was integrated to yield a continuous tidal volume, and the measurements of total lung resistance ( $R_t$ ) and dynamic compliance ( $C_{dyn}$ ) were made at isovolumetric and zero flow points. The flow, volume and pressure were recorded on an eight channel Gould 2000 W high-frequency recorder and  $C_{dyn}$  was calculated using the total volume and the difference in  $P_{tp}$  at zero flow, and  $R_t$  was calculated as the ratio of  $P_{tp}$  and V at midtidal lung volumes. These calculations were made automatically with the Buxco automated pulmonary mechanics respiratory analyzer (Model 6, Buxco Electronics, Sharon, CT), as previously described by Giles et al. See, Giles et al., Arch. Int. Pharmacodyn. Ther. 194: 213-232 (1971), the relevant portion of which describing these calculations is incorporated in toto hereby by reference. The results obtained upon administration of oligo II on allergic rabbits are shown and discussed in Example 26 below.

**Example 14: Measurement of Bronchial Hyperresponsiveness (BHR)**

Each allergic rabbit was administered histamine by aerosol to determine their baseline hyperresponsiveness. Aerosols of either saline or histamine were generated using a DeVilbiss nebulizer (DeVilbiss, Somerset, PA) for 30 seconds and then for 2 minutes at each dose employed. The ultrasonic nebulizer produced aerosol droplets of which 80% were <5 micron in diameter. The histamine aerosol was administered in increasing concentrations (0.156 to 80 mg/ml) and measurements of pulmonary function were made after each dose. The B4R was then determined by calculating the concentration of histamine (mg/ml) required to reduce the  $C_{dyn}$  50% from baseline ( $PC_{50}$  Histamine).

**Example 15: Cardiovascular Effect of Anti-sense Oligo I**

The measurement of cardiac output and other cardiovascular parameters using CardiomaxJ utilizes the principal of thermal dilution in which the change in temperature of the blood exiting the heart after a venous injection of a known volume of cool saline is monitored. A single rapid injection of cool saline was made into the right atrium via cannulation of the right jugular vein, and the corresponding changes in temperature of the mixed injectate and blood in the aortic arch were recorded via cannulation of the carotid artery by a temperature-sensing miniprobe. Twelve hours after the allergic rabbits had been treated with aerosols of oligo I (EPI 2010; SEQ ID NO: 9370) as described in (d) above, the animals were anesthetized with 0.3 ml/kg of 80% Ketamine and 20% Xylazine. This time point coincides with previous data showing efficacy for SEQ ID NO: 9370, as is clearly shown by Nyce & Metzger, (1997), supra, the pertinent disclosure being incorporated in its entirety here by reference. A thermocouple was then inserted into the left carotid artery of each rabbit, and was then advanced 6.5 cm and secured with a silk ligature. The right jugular vein was then cannulated and a length of polyethylene tubing was inserted and secured. A thermodilution curve was then established on a CardiomaxJ II (Columbus Instruments, Ohio) by injecting sterile saline at 20EC to determine the correctness of positioning of the thermocouple probe. After establishing the correctness of the position of the thermocouple, the femoral artery and vein were isolated. The femoral vein was used as a portal for drug injections, and the femoral artery for blood pressure and heart rate measurements. Once constant baseline cardiovascular parameters were established, CardiomaxJ measurements of blood pressure, heart rate, cardiac output, total peripheral resistance, and cardiac contractility were made.

**Example 16: Duration of Action of Oligo I (SEQ ID NO: 9370)**

Eight allergic rabbits received initially increasing log doses of adenosine by means of a nebulizer via an intra-tracheal tube as described in (f) above, beginning with 0.156 mg/ml until compliance was reduced by 50% ( $PC_{50}$  Adenosine) to establish a baseline. Six of the rabbits then received four 5 mg aerosolized doses of (SEQ ID NO: 9370) as described above. Two rabbits received equivalent amounts of saline vehicle as controls. Beginning 18 hours after the last treatment, the  $PC_{50}$  Adenosine values were tested again. After this point, the measurements were continued for all animals each day, for up to 10 days. The results of this study are discussed in Example 25 below.

**Example 17: Reduction of Adenosine  $A_{2b}$  Receptor Number by Anti-sense Oligo V**

Sprague Dawley rats were administered 2.0 mg respirable anti-sense oligo V (SEQ ID NO:9379) three times over two days using an inhalation chamber as described above. Twelve hours after the last administration, lung parenchymal tissue was dissected and assayed for adenosine  $A_{2b}$  receptor binding using [311]-NECA as described by Nyce & Metzger (1997), supra. Controls were conducted by administration of equal volumes of saline.



The results are significant at  $p < 0.05$  using Student's paired t test, and are discussed in Example 28 below.

**Example 18: Comparison of Oligo I & Corresponding  
Phosphodiester Oligo VI (SEQ ID NO:11050)**

Oligo I (SEQ ID NO:9370) countered the effects of adenosine and eliminated sensitivity to it for adenosine amount up to 20 mg adenosine/5.0 ml (the limit of solubility of adenosine). Oligo VI (SEQ ID NO: 11050), the phosphodiester version of the oligonucleotide sequence, was completely ineffective when tested in the same manner. Both compounds have identical sequence, differing only in the presence of phosphorothioate residues in Oligo I (SEQ ID NO:9370), and were delivered as an aerosol as described above and in Nyce & Metzger (1997), supra. Significantly different at  $p < 0.001$ , Student's paired t test. The results are discussed in Example 29 below.

**RESULTS OBTAINED FOR ANTI-SENSE OLIGO I (SEQ ID NO: 1)**

**Example 19: Results of Prior Work**

The nucleotide sequence and other data for anti-sense oligo I (SEQ ID NO: 9370), which is specific for the adenosine A<sub>1</sub> receptor, were provided above. The experimental data showing the effectiveness of oligo I in down regulating the receptor number and activity were also provided above. Further information on the characteristics and activities of anti-sense oligo I is provided in Nyce, J. W. and Metzger, W. J., Nature 385:721 (1997), the relevant parts of which relating to the following results are incorporated in their entireties herein by reference. The Nyce & Metzger (1997) publication provided data showing that the anti-sense oligo I (SEQ ID NO: 9370):

- (1) The anti-sense oligo I reduces the number of adenosine A<sub>1</sub> receptors in the bronchial smooth muscle of allergic rabbits in a dose-dependent manner as may be seen in Table 5 below.
- (2) Anti-sense Oligo I attenuates adenosine-induced bronchoconstriction and allergen-induced bronchoconstriction.
- (3) The Oligo I attenuates bronchial hyperresponsiveness as measured by PC<sub>50</sub> histamine, a standard measurement to assess bronchial hyperresponsiveness. This result clearly demonstrates anti-inflammatory activity of the anti-sense oligo I as is shown in Table 5 above.
- (4) As expected, because it was designed to target it, the anti-sense oligo I is totally specific for the adenosine A<sub>1</sub> receptor, and has no effect at all at any dose on either the very closely related adenosine A<sub>2</sub> receptor or the related bradykinin B<sub>2</sub> receptor. This is seen in Table 5 below.
- (5) In contradistinction to the above effects of the Oligo I, the mismatch control molecules MM2 and MM3 (SEQ ID NO:11051 and SEQ ID NO:11052) which have identical base composition and molecular weight but differed from the anti-sense oligo I (SEQ ID NO: 9370) by 6 and 2 mismatches, respectively. These mismatches, which are the minimum possible while still retaining identical base composition, produced absolutely no effect upon any of the targeted receptors (A<sub>1</sub>, A<sub>2</sub> or B<sub>2</sub>).

These results, along with a complete lack of prior art on the use of anti-sense oligonucleotides, such as oligo I, targeted to the adenosine A<sub>1</sub> receptor, are unexpected results. The showings presented in this patent clearly enable and demonstrate the effectiveness, for their intended use, of the claimed agents and method for treating a disease or condition associated with lung airway, such as bronchoconstriction, inflammation, allergy(ies), and the like.

**Example 20: Oligo I Significantly Reduces  
Response to Adenosine Challenge**

The receptor binding experiment is described in Example 12 above, and the results shown in Table 5 below which shows the binding characteristics of the adenosine A<sub>1</sub>-selective ligand [<sup>3</sup>H]DPCPX and the bradykinin B<sub>2</sub>-selective ligand [<sup>3</sup>H]NPC 17731 in membranes isolated from airway smooth muscle of A<sub>1</sub> adenosine receptor and B<sub>2</sub> bradykinin receptor anti-sense- and mismatch-treated allergic rabbits.

**Table 5: Binding Characteristics of Three Anti-Sense Oligos**

Treatment <sup>1</sup>	A <sub>1</sub> receptor		B <sub>2</sub> receptor	
	Kd	B <sub>max</sub>	Kd	B <sub>max</sub>

Adenosine A <sub>1</sub>	Receptor			
20 mg	0.36±0.029 nM	19±1.52 fmoles*	0.39±0.031 nM	14.8±0.99 fmoles
2 mg	0.38±0.030 nM	32±2.56 fmoles*	0.41±0.028 nM	15.5±1.08 fmoles
0.2 mg	0.37±0.030 nM	49±3.43 fmoles	0.34±0.024 nM	15.0±1.06 fmoles
<b>A<sub>1</sub>MM1</b>	<b>(Control)</b>			
20 mg	0.34±0.027 nM	52.0±3.64 fmoles	0.35±0.024 nM	14.0±1.0 fmoles
2 mg	0.37±0.033 nM	51.8±3.88 fmoles	0.38±0.028 nM	14.6±1.02 fmoles
<b>B<sub>2</sub>A (Bradykinin</b>	<b>Receptor)</b>			
20 mg	0.36±0.028 nM	45.0±3.15 fmoles	0.38±0.027 nM	8.7±0.62 fmoles*
2 mg	0.39±0.035 nM	44.3±2.90 fmoles	0.34±0.024 nM	11.9±0.76
0.2 mg	0.40±0.028 nM	47.0±3.76 fmoles	0.35±0.028 nM	15.1±1.05 fmoles
<b>B<sub>2</sub>MM (Control)</b>				
20 mg	0.39±0.031 nM	42.0±2.94 fmoles	0.41±0.029 nM	14.0±0.98 fmoles
2 mg	0.41±0.035 nM	40.0±3.20 fmoles	0.37±0.030 nM	14.8±0.99 fmoles
0.2 mg	0.37±0.029 nM	43.0±3.14 fmoles	0.36±0.025 nM	15.1±1.35 fmoles
Saline Control	0.37±0.041	46.0±5.21	0.39±0.047 nM	14.2±1.35 fmoles

**Example 21: Dose-response Effect of Oligo I**

Anti-sense oligo I (SEQ ID NO:9370) was found to reduce the effect of adenosine administration to the animal in a dose-dependent manner over the dose range tested as shown in Table 6 below.

**Table 6: Dose-Response Effect to Anti-sense Oligo I**

Total Dose (mg)	PC <sub>50</sub> Adenosine (mg Adenosine)
<b>Anti-sense Oligo I</b>	
0.2	8.32±7.2
2.0	14.0±7.2
20	19.5±0.34
<b>A<sub>1</sub>MM2 oligo (control)</b>	
0.2	2.51±0.46
2.0	3.13± 0.71
20	3.25± 0.34

The above results were studied with the Student's paired t test and found to be statistically different, p=0.05

The oligo I (SEQ ID NO:9370), an anti-adenosine A<sub>1</sub> receptor oligo, acts specifically on the adenosine A<sub>1</sub> receptor, but not on the adenosine A<sub>2</sub> receptors. These results stem from the treatment of rabbits with anti-sense oligo I (SEQ ID NO: 9370) or mismatch control oligo (SEQ ID NO:11051; A<sub>1</sub>MM2) as described in Example 9 above and in Nyce & Metzger (1997), supra (four doses of 5 mg spaced 8 to 12 hours apart via nebulizer via endotracheal tube), bronchial smooth muscle tissue excised and the number of adenosine A<sub>1</sub> and adenosine A<sub>2</sub> receptors determined as reported in Nyce & Metzger (1997), supra.

**Example 22: Specificity of Oligo I (SEQ ID NO:9370) for Target Gene Product**

Oligo I (SEQ ID NO:9370) is specific for the adenosine A<sub>1</sub> receptor whereas its mismatch controls had no activity. Figure 1 depicts the results obtained from the cross-over experiment described in Example 10 above and in Nyce & Metzger (1997), supra. The two mismatch controls (SEQ ID NO:11051 and SEQ ID NO:11052) evidenced no effect on the PC<sub>50</sub> Adenosine value. On the contrary, the administration of anti-sense oligo I (SEQ ID NO:9370) showed a seven-fold increase in the PC<sub>50</sub> Adenosine value. The results clearly indicate that the anti-sense oligo I (SEQ ID NO: 9370) reduces the response (attenuates the sensitivity) to exogenously administered adenosine

when compared with a saline control. The results provided in Table 6 above clearly establish that the effect of the anti-sense oligo I is dose dependent (see, column 3 of Table 5). The Oligo I was also shown to be totally specific for the adenosine A<sub>1</sub> receptor, (see, top 3 rows of Table), inducing no activity at either the closely related adenosine A<sub>2</sub> receptor or the bradykinin B<sub>2</sub> receptor (see, lines 8-10 of Table 6 above). In addition, the results shown in Table 6 establish that the anti-sense oligo I (SEQ ID NO:9370) decreases sensitivity to adenosine in a dose dependent manner, and that it does this in an anti-sense oligo-dependent manner since neither of two mismatch control oligonucleotides (A<sub>1</sub>MM2; SEQ ID NO:11051 and A<sub>1</sub>MM3; SEQ ID NO:11052) show any effect on PC<sub>50</sub> Adenosine values or on attenuating the number of adenosine A<sub>1</sub> receptors.

**Example 23: Effect on Aeroallergen-induced  
Bronchoconstriction & Inflammation**

The Oligo I (SEQ ID NO:9370) was shown to significantly reduce the histamine-induced effect in the rabbit model when compared to the mismatch oligos. The effect of the anti-sense Oligo I (SEQ ID NO:9370) and the mismatch oligos (A<sub>1</sub>MM2, SEQ ID NO:11051 and A<sub>1</sub>MM3, SEQ ID NO:11051) on allergen-induced airway obstruction and bronchial hyperresponsiveness was assessed in allergic rabbits. The effect of the anti-sense oligo I (SEQ ID NO:9370) on allergen-induced airway obstruction was assessed. As calculated from the area under the plotted curve, the anti-sense oligo I significantly inhibited allergen-induced airway obstruction when compared with the mismatched control (55%, p<0.05; repeated measures ANOVA, and Tukey's t test). A complete lack of effect was induced by the mismatch oligo A<sub>1</sub>MM2 (Control) on allergen induced airway obstruction. The effect of the anti-sense oligo I (SEQ ID NO:9370) on allergen-induced BHR was determined as above. As calculated from the PC<sub>50</sub> Histamine value, the anti-sense oligo I (SEQ ID NO:9370) significantly inhibited allergen-induced BHR in allergic rabbits when compared to the mismatched control (61%, p<0.05; repeated measures ANOVA, Tukey's t test). A complete lack of effect of the A<sub>1</sub>MM mismatch control on allergen-induced BHR was observed. The results indicated that anti-sense oligo I (SEQ ID NO: 9370) is effective to protect against aeroallergen-induced bronchoconstriction (house dust mite). In addition, the anti-sense oligo I (SEQ ID NO:9370) was also found to be a potent inhibitor of dust mite-induced bronchial hyper responsiveness, as shown by its effects upon histamine sensitivity which indicates anti-inflammatory activity for anti-sense oligo I (SEQ ID NO:1). The results indicated that anti-sense oligo I (SEQ ID NO 9370) is effective to protect against aeroallergen-induced bronchoconstriction (house dust mite). In addition, the anti-sense oligo I (SEQ ID NO: 9370) was also found to be a potent inhibitor of dust mite-induced bronchial hyper responsiveness, as shown by its effects upon histamine sensitivity which indicates anti-inflammatory activity for anti-sense oligo I (SEQ ID NO: 9370). The results indicated that anti-sense oligo I (SEQ ID NO: 9370) is effective to protect against aeroallergen-induced bronchoconstriction (house dust mite). In addition, the anti-sense oligo I (SEQ ID NO: 9370) was also found to be a potent inhibitor of dust mite-induced bronchial hyper responsiveness, as shown by its effects upon histamine sensitivity which indicates anti-inflammatory activity for anti-sense oligo I (SEQ ID NO: 9370). The results indicated that anti-sense oligo I (SEQ ID NO: 9370) is effective to protect against aeroallergen-induced bronchoconstriction (house dust mite). In addition, the anti-sense oligo I (SEQ ID NO: 9370) was also found to be a potent inhibitor of dust mite-induced bronchial hyper responsiveness, as shown by its effects upon histamine sensitivity which indicates anti-inflammatory activity for anti-sense oligo I (SEQ ID NO: 9370). The results indicated that anti-sense oligo I (SEQ ID NO: 9370) is effective to protect against aeroallergen-induced bronchoconstriction (house dust mite). In addition, the anti-sense oligo I (SEQ ID NO: 9370) was also found to be a potent inhibitor of dust mite-induced bronchial hyper responsiveness, as shown by its effects upon histamine sensitivity which indicates anti-inflammatory activity for anti-sense oligo I (SEQ ID NO: 9370).

**Example 24: Anti-sense Oligo I is Free  
of Deleterious Side Effects**

The Oligo I (SEQ ID NO: 9370) was shown to be free of side effects that might be toxic to the recipient. No changes in arterial blood pressure, cardiac output, stroke volume, heart rate, total peripheral resistance or heart

contractility (dPdT) were observed following administration of 2.0 or 20 mg oligo I (SEQ ID NO: 9370). The addition, the results of the measurement of cardiac output (CO), stroke volume (SV), mean arterial pressure (MAP), heart rate (HR), total peripheral resistance (TPR), and contractility (dPdT) with a CardiomaxJ apparatus (Columbus Instruments, Ohio) were assessed. These results evidenced that oligo I (SEQ ID NO: 9370) has no detrimental effect upon critical cardiovascular parameters. More particularly, this oligo does not cause hypotension. This finding is of particular importance because other phosphorothioate anti-sense oligonucleotides have been shown in the past to induce hypotension in some model systems. Furthermore, the adenosine A<sub>1</sub> receptor plays an important role in sinoatrial conduction within the heart. Attenuation of the adenosine A<sub>1</sub> receptor by anti-sense oligo I (SEQ ID NO: 9370) might be expected to result, therefore, in deleterious extrapulmonary activity in response to the downregulation of the receptor. This is not the case. The anti-sense oligo I (SEQ ID NO: 9370) does not produce any deleterious intrapulmonary effects and renders the administration of the low doses of the present anti-sense oligo free of unexpected, undesirable side effects. This demonstrates that when oligo I (SEQ ID NO: 9370) is administered directly to the lung, it does not reach the heart in significant quantities to cause deleterious effects. This is in contrast to traditional adenosine receptor antagonists like theophylline which do escape the lung and can cause deleterious, even life-threatening effects outside the lung.

**Example 25: Long Lasting Effect of Oligo I**

The Oligo I (SEQ ID NO: 9370) evidenced a long lasting effect as evidenced by the PC<sub>50</sub> and Resistance values obtained upon its administration prior to adenosine challenge. The duration of the effect was measured for with respect to the PC<sub>50</sub> of adenosine anti-sense oligo I when administered in four equal doses of 5 mg each by means of a nebulizer via an endotracheal tube, as described above. The effect of the agent is significant over days 1 to 8 after administration. When the effect of the anti-sense oligo I (SEQ ID NO: 9370) had disappeared, the animals were administered saline aerosols (controls), and the PC<sub>50</sub> Adenosine values for all animals were measured again. Saline-treated animals showed base line PC<sub>50</sub> adenosine values (n=6). The duration of the effect (with respect to Resistance) was measured for six allergic rabbits which were administered 20 mg of anti-sense oligo I (SEQ ID NO: 9370) as described above, upon airway resistance measured as also described above. The mean calculated duration of effect was 8.3 days for both PC<sub>50</sub> adenosine (p<0.05) and resistance (p<0.05). These results show that anti-sense oligo I (SEQ ID NO: 9370) has an extremely long duration of action, which is completely unexpected.

**Example 26: Anti-sense Oligo II**

Anti-sense oligo II, targeted to a different region of the adenosine A<sub>1</sub> receptor mRNA, was found to be highly active against the adenosine A<sub>1</sub>-mediated effects. The experiment measured the effect of the administration of anti-sense oligo II (SEQ ID NO: 9376) upon compliance and resistance values when 20 mg anti-sense oligo II or saline (control) were administered to two groups of allergic rabbits as described above. Compliance and resistance values were measured following an administration of adenosine or saline as described above in Example 13. The effect of the anti-sense oligo of the invention was different from the control in a statistically significant manner, p<0.05 using paired t-test, compliance; p<0.01 for resistance. The results showed that anti-sense oligo II (SEQ ID NO: 9376), which targets the adenosine A<sub>1</sub> receptor, effectively maintains compliance and reduces resistance upon adenosine challenge.

**Example 27: Antisense Oligos III and IV**

Oligos III (SEQ ID NO: 9377) and IV (SEQ ID NO: 9378) were shown to be in fact specifically targeted to the adenosine A<sub>3</sub> receptor by their effect on reducing inflammation and the number of inflammatory cells present upon separate administration of 20 mg of the anti-sense oligos III (SEQ ID NO: 9377) and IV (SEQ ID NO: 9378) to allergic rabbits as described above. The number of inflammatory cells was determined in their bronchial lavage fluid 3 hours later by counting at least 100 viable cells per lavage. The effect of anti-sense oligos III (SEQ ID NO: 9377) and IV (SEQ ID NO: 9378) upon granulocytes, and upon total cells in bronchial lavage were assessed following exposure to dust mite allergen. The results showed that the anti-sense oligo IV (SEQ ID NO: 9378) and anti-sense oligo III (SEQ ID NO: 9377) are very potent anti-inflammatory agents in the asthmatic lung following exposure to dust mite allergen. As is known in the art, granulocytes, especially eosinophils, are the primary inflammatory cells of asthma, and the administration of anti-sense oligos III (SEQ ID NO: 9377) and IV (SEQ ID NO: 9378) reduced their numbers by 40% and 66%, respectively. Furthermore, anti-sense oligos IV (SEQ ID NO: 9378) and III (SEQ ID NO: 9376) also reduced the total number of cells in the bronchial lavage fluid by 40% and

80%, respectively. This is also an important indicator of anti-inflammatory activity by the present anti-adenosine A<sub>3</sub> agents of the invention. Inflammation is known to underlie bronchial hyperresponsiveness and allergen-induced bronchoconstriction in asthma. Both anti-sense oligonucleotides III (SEQ ID NO: 9377) and IV (SEQ ID NO: 9378), which are targeted to the adenosine A<sub>3</sub> receptor, are representative of an important new class of anti-inflammatory agents which may be designed to specifically target the lung receptors of each species.

**Example 28: Anti-sense Oligo V**

The anti-sense oligo V (SEQ ID NO: 9379), targeted to the adenosine A<sub>2b</sub> adenosine receptor mRNA was shown to be highly effective at countering adenosine A<sub>2b</sub>-mediated effects and at reducing the number of adenosine A<sub>2b</sub> receptors present to less than half.

**Example 29: Unexpected Superiority of Substituted over Phosphodiester-residue Oligo I-DS (SEQ ID NO:1681)**

Oligos I (SEQ ID NO: 9370) and I-DS (SEQ ID NO: 11050) were separately administered to allergic rabbits as described above, and the rabbits were then challenged with adenosine. The phosphodiester oligo I-DS (SEQ ID NO: 11050) was statistically significantly less effective in countering the effect of adenosine whereas oligo I (SEQ ID NO: 9370) showed high effectiveness, evidencing a PC<sub>50</sub> Adenosine of 20 mg.

**Example 30: Anti-sense Oligo VI**

For the present work, I designed an additional anti-sense phosphorothioate oligo targeted to the adenosine A<sub>1</sub> receptor (Oligo VI). This anti-sense oligo was designed for therapy on a selected species as described in the above patent application and is generally specific for that species, unless the segment of the adenosine receptor mRNA of other species elected happens to have a similar sequence. The anti-sense oligos were prepared as described below, and tested in vivo in a rabbit model for bronchoconstriction, inflammation and lung allergy, which have breathing difficulties and impeded lung airways, as is the case in ailments such as asthma, as described in the above-identified application. One additional oligo and its effect in a rabbit model was studied and the results of the study are reported and discussed below. The present oligo (anti-sense oligo VI) was selected for this study to complement the data on SEQ ID NO: 1 (Oligo I), which is anti-sense to the adenosine A<sub>1</sub> receptor mRNA provided in the above-identified patent application. This additional oligo is identified as anti-sense Oligo VI, and is targeted to a different region of the adenosine A<sub>1</sub> receptor mRNA than Oligo I. The design and synthesis of this anti-sense oligo was performed in accordance with the teaching, particularly Example 1, of the above-identified patent application. The anti-sense Oligo VI is a phosphorothioate designed to target the coding region of the rabbit adenosine A<sub>1</sub> receptor mRNA region +964 to +984 relative to the initiation codon (start site). The Oligo VI was prepared as described in the above-indicated application, and is 20 nucleotides long. The Oligo VI is directed to the adenosine A<sub>1</sub> receptor gene, and has the following sequence: 5'-CGC CGG CGG GTG CGG GCC GG-3' (SEQ ID NO: 12491). The phosphorothioate anti-sense Oligo VI having the sequence described in (5) above, was synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, DE). TETD (tetraethylthiuram disulfide) was used as the sulfurizing agent during the synthesis.

**Example 31: Preparation of Allergic Rabbits**

Neonatal New Zealand white Pasturella-free rabbits were immunized intraperitoneally within 24 hours of birth with 0.5 ml of 312 antigen units/ml house dust mite (*D. farinae*) extract (Berkeley Biologicals, Berkeley, CA) mixed with 10% kaolin as previously described (Metzger, W. J., in Late Phase Allergic Reactions, Dorsch, W., Ed., CRC Handbook, pp 347-362, CRC Press, Boca Raton, 1990; Ali, S. Et al., Am. J. Resp. Crit. Care Med. 149: 908 (1994)). The immunizations were repeated weekly for the first month and then bi-weekly until the animals were 4 months old. These rabbits preferentially produce allergen-specific IgE antibody, typically respond to aeroallergen challenge with both an early and late-phase asthmatic response, and show bronchial hyper responsiveness (BHR). Monthly intraperitoneal administration of allergen (312 units dust mite allergen, as above) continues to stimulate and maintain allergen-specific IgE antibody and BHR. At 4 months of age, sensitized rabbits were prepared for aerosol administration as described by Ali et al. (1994), supra.

**Example 32: Adenosine Aerosol Preparation**

An adenosine aerosol (20 mg/ml) was prepared with an ultrasonic nebulizer (Model 646, DeVilbiss, Somerset, PA), which produced aerosol droplets, 80% of which were smaller than 5:μm in diameter. Equal volumes of the aerosols were administered directly to the lungs via an intratracheal tube to all three rabbits. The animals were then administered the aerosolized adenosine and Day 1 pre-treatment values for sensitivity to adenosine were calculated as the dose of adenosine causing a 50% loss of compliance (PC<sub>50</sub> Adenosine). The animals were then administered the aerosolized anti-sense via the intratracheal tube (5 mg/1.0 ml), for 2 minutes, twice daily for 2 days (total dose, 20 mg). Post-treatment PC<sub>50</sub> values were recorded (post-treatment challenge) on the morning of the third day. The results of these studies are provided in (9) below.

**Example 33: Anti-sense Oligo Formulation**

Each one of anti-sense oligos were separately solubilized in an aqueous solution and administered as described for anti-sense oligo I in (e) above, in four 5 mg aliquots (20 mg total dose) by means of a nebulizer via endotracheal tube, as described above.

**Example 34: Oligo VI Reduces Response to Adenosine Challenge as well or Better than Oligo I**

Oligo VI was tested in three allergic rabbits of the characteristics and readied as described in (7) above and in the above-indicated patent application. Oligo VI targets a section of the coding region of the A<sub>1</sub> receptor which is different from Oligo I. Both these target sequences were selected randomly from many possible coding region target sequences. The three rabbits were treated identically as previously indicated for Oligo I. Briefly, 5 mg of Oligo VI were nebulized to the rabbits twice per day at 8 hour intervals, for two days. Thereafter, PC<sub>50</sub> adenosine studies were performed on the morning of the third day and compared to pre-treatment PC<sub>50</sub> values. This protocol is described in more detail in Nyce and Metzger (Nyce & Metzger, Nature 385: 721-725 (1997)). The results obtained for the three rabbits are shown in Table 7 below.

**Table 7: PC<sub>50</sub> Adenosine before & after Aerosolized Adenosine Treatment**

Treatment Time	PC <sub>50</sub> Adenosine (mg)
Pre-treatment	3.0 ±2.1
Post-treatment	>20.0*
* maximum achievable dose due to adenosine insolubility in saline	

All three animals treated with Oligo VI completely eliminated sensitivity to adenosine up to the measurable level of the agent shown in Table 7 above. That is, the administration of the Oligo VI abrogated the adenosine-induced bronchoconstriction in the three allergic rabbits. The actual efficacy of Oligo VI is, therefore, greater than could be measured in the experimental system used. By comparing with the previously submitted results for the Oligo I, it may be seen that the Oligo VI was found to be as effective, or more, than Oligo I.

**Example 34: Conclusions**

The work described and results discussed in the examples clearly indicates that all anti-sense oligonucleotides designed in accordance with the teachings of the above-identified application were found to be highly effective at countering or reducing effects mediated by the receptors they are targeted to. That is, each and all of the two anti-sense oligos targeting an adenosine A<sub>1</sub> receptor mRNA, 1 anti-sense oligo targeting an adenosine A<sub>2b</sub> receptor mRNA, and the 2 anti-sense oligos targeting an A<sub>3</sub> receptor mRNA were shown capable of countering the effect of exogenously administered adenosine which is mediated by the specific receptor they are targeted to. The activity of the anti-sense oligos of this invention, moreover, is specific to the target and substitutively fails to inhibit another target. In addition, the results presented also show that the administration of the present agents results in extremely low or non-existent deleterious side effects or toxicity. This represents 100% success in providing agents that are highly effective and specific in the treatment of bronchoconstriction and/or inflammation. This invention is broadly applicable in the same manner to all gene(s) and corresponding mRNAs encoding proteins involved in or associated with airway diseases. A comparison of the phosphodiester and a version of the same oligonucleotide wherein the phosphodiester bonds are substituted with phosphorothioate bonds evidenced an unexpected superiority for the phosphothiorate oligonucleotide over the phosphodiester anti-sense oligo.

**Example 35: In Vivo Response to Adenosine Challenge**

### with & without Oligo I Pretreatment

Two hyper responsive monkeys (ascaris sensitive) were challenged with inhaled adenosine, with and without pre-treatment with anti-sense oligo I (SEQ ID NO: 9370). The PC<sub>40</sub> adenosine was calculated from the data collected as being equivalent to that amount of adenosine in mg that causes a 40% decrease in dynamic compliance in hyper-responsive airways. The Oligo I (SEQ ID NO: 9370; EPI 2010) was subsequently administered at 10 mg/day for 2 days by inhalation. On the third day, the PC adenosine was again measured. The PC<sub>40</sub> adenosine value prior to treatment with Oligo I was compared side-by-side with to the PC<sub>40</sub> adenosine taken after administration of Oligo I (Figure not shown). The results of the experiment conducted with two animals showed that any sensitivity to adenosine was completely eliminated by the administration of the oligo of this invention in one animal, and substantially reduced in the second.

### Example 36: Extension of the experimental Results

The method of the present invention is also practiced with anti-sense oligonucleotides targeted to many genes, mRNAs and their corresponding proteins as described above, in essentially the same manner as given above, for the treatment of various conditions in the lungs. Examples of these are Human A<sub>2a</sub> adenosine receptor, Human A<sub>2b</sub> adenosine receptor, Human IgE receptor  $\beta$ , Human Fc-epsilon receptor CD23 antigen (IgE receptor), Human IgE receptor,  $\alpha$  subunit, Human IgE receptor, Fc epsilon R, Human histidine decarboxylase, Human beta tryptase, Human tryptase-I, Human prostaglandin D synthase, Human cyclooxygenase-2, Human eosinophil cationic protein, Human eosinophil derived neurotoxin, Human eosinophil peroxidase, Human intercellular adhesion molecule-1 (ICAM-1), Human vascular cell adhesion molecule 1 (VCAM-1), Human endothelial leukocyte adhesion molecule (ELAM-1), Human P Selectin, Human endothelial monocyte activating factor, Human IL3, Human IL4, Human IL5, Human IL6, Human monocyte-derived neutrophil chemotactic factor, Human neutrophil elastase (medullasin), Human neutrophil oxidase factor, Human cathepsin G, Human defensin 1, Human defensin 3, Human macrophage inflammatory protein-1-alpha, Human muscarinic acetylcholine receptor HM1, Human muscarinic acetylcholine receptor HM3, Human fibronectin, Human interleukin 8, Human GM-CSF, Human tumor necrosis factor  $\alpha$ , Human leukotriene C4 synthase, Human major basic protein, and many more.

### Example 37: In Vivo Effects of Folinic Acid and DHEA on Adenosine Levels

In the examples provided below, EA means an epiandrosterone, DHEA means dehydroepiandrosterone, s means seconds, mg means milligrams, kg means kilograms, kw means kilowatts, Mhz means megahertz, CoQ means a ubiquinone, and nmol means nanomoles.

Young adult male Fischer 344 rats (120 grams) were administered dehydroepiandrosterone (DHEA) (300 mg/kg) or methyltestosterone (40 mg/kg) in carboxymethylcellulose by gavage once daily for fourteen days. Folinic acid (50 mg/kg) was administered intraperitoneally once daily for fourteen days. On the fifteenth day, the animals were sacrificed by microwave pulse (1.33 kw, 2450 MHZ, 6.5 s) to the cranium, which instantly denatures all brain protein and prevents further metabolism of adenosine. Hearts were removed from animals and flash frozen in liquid nitrogen with 10 seconds of death. Liver and lungs were removed en bloc and flash frozen with 30 seconds of death. Brain tissue was subsequently dissected. Tissue adenosine was extracted, derivatized to 1, N6-ethenoadenosine and analyzed by high performance liquid chromatography (HPLC) using spectrofluorometric detection according to the method of Clark and Dar (J. of Neuroscience Methods 25:243 (1988)). Results of these experiments are summarized in Table 1 below. Results are expressed as the mean  $\pm$  SEM, with ? p<0.05 compared to control group and  $\psi$  p<0.05 compared to DHEA or methyltestosterone-treated groups.



**Table 1: In Vivo Effect of DHEA,  $\delta$ -1-methyltestosterone & Folinic Acid on Adenosine Levels in Various Rat Tissues**

	Intracellular Adenosine (nmol/mg protein)		
	Heart	Lung	Brain
Control	10.6 $\pm$ 0.6 (n=12)	3.1 $\pm$ 0. (n=6)	0.5 $\pm$ 0.04 (n=12)
DHEA (300 mg/kg)	6.7 $\pm$ 0.5 (n=12)	2.3 $\pm$ 0.3 (n=6)	0.19 $\pm$ 0.01 (n=12)
Methyltestosterone (40 mg/kg)	8.3 $\pm$ 1.0 (n=6)	N.D.	0.42 $\pm$ 0.06 (n=6)
Methyltestost. (M) (120mg/kg)	6.0 $\pm$ 0.4 (n=6)	N.D.	0.32 $\pm$ 0.03 (n=6)
Folinic Acid (F.A.) (50mg/kg)	12.4 $\pm$ 2.1 (n=5)	N.D.	0.72 $\pm$ 0.09 (n=5)
DHEA+ F.A. (300mg/kg;50mg/kg)	11.1 $\pm$ 0.6 (n=5)	N.D.	0.55 $\pm$ 0.09 (n=5)
M + F.A. (120mg/kg;50mg/kg)	9.1 $\pm$ 0.4 (n=6)	N.D.	0.60 $\pm$ 0.06 (n=6)
N.D. = Not Determined			

The results of these experiments indicate that rats administered DHEA or methyltestosterone daily for two weeks showed multi-organ depletion of adenosine. Depletion was dramatic in brain (60% depletion for DHEA, 34% for high dose methyltestosterone) and heart (37% depletion for DHEA, 22% depletion for high dose methyltestosterone). Co-administration of folinic acid completely abrogated steroid-mediated adenosine depletion. Folinic acid administered alone induce increase in adenosine levels for all organs studied.

#### **Example 38: Preparation of the Experimental Model**

Cell cultures, HT-29 SF cells, which represent a subline of HY-29 cells (ATCC, Rockville, Md.) and are adapted for growth in completely defined serum-free PC-1 medium (Ventrex, Portland, Me.), were obtained. Stock cultures were maintained in this medium at 37° in a humidified atmosphere containing 5% CO<sub>2</sub>. At confluence cultures were replated after dissociation using trypsin/EDTA (Gibco, Grand Island, N.Y.) and re-fed every 24 hours. Under these conditions, the doubling time for HT-29 SF cells during logarithmic growth was 24 hours.

#### **Example 39: Flow Cytometry**

Cells were plated at 10<sup>5</sup>/60-mm dish in duplicate. For analysis of cell cycle distribution, cultures were exposed to either 0, 25, 50, or 200  $\mu$ M DHEA. For analysis of reversal of cell cycle effects of DHEA, cultures were exposed to either 0 or 25  $\mu$ M DHEA, and the media were supplemented with MVA, CH, RN, MVA plus CH, or MVA plus CH plus RN or were not supplemented. Cultures were trypsinized following 0, 24, 48, or 74 hours and fixed and stained using a modification of a procedure of Bauer et al., *Cancer Res.*, 46, 3173-3178 (1986). Briefly, cells were collected by centrifugation and resuspended in cold phosphate-buffered saline. Cells were fixed in 70% ethanol, washed, and resuspended in phosphate-buffered saline. One ml hypotonic stain solution [50  $\mu$ g/ml propidium iodide (Sigma Chemical Co.), 20  $\mu$ g/ml Rnase A (Boehringer Mannheim, Indianapolis, Ind.), 30 mg/ml polyethylene glycol, 0.1% Triton X-100 in 5 mM citrate buffer] was then added, and after 10 min at room temperature, 1 ml of isotonic stain solution [propidium iodide, polyethylene glycol, Triton X-100 in 0.4M NaCl] was added and the cells were analyzed using a flow cytometer, equipped with pulse width/pulse area doublet discrimination (Becton Dickinson Immunocytometry Systems, San Jose, Calif.) After calibration with fluorescent beads, a minimum of 2x10<sup>4</sup> cells/sample were analyzed, data were displayed as total number of cells in each of 1024 channels of increasing fluorescence intensity, and the resulting histogram was analyzed using the Cellfit analysis program (Becton Dickinson).

#### **Example 40: DHEA Effect on Cell Growth**

Cells were plated 25,000 cells/30 mm dish in quadruplicate, and after 2 days received 0, 12.5, 25, 50, or 200  $\mu$ M DHEA. Cell number was determined 0, 24, 48, and 72 hours later using a Coulter counter (model Z, Coulter Electronics, Inc. Hialeah, Fla.). DHEA (AKZO, Basel, Switzerland) was dissolved in dimethyl sulfoxide,

filter sterilized, and stored at -20°C until use.

Figure 1 illustrates the inhibition of growth for HT-29 cells by DHEA. Points refer to numbers of cells, and bars refer to SEM. Each data point was performed in quadruplicate, and the experiment was repeated three times. Where SEM bars are not apparent, SEM was smaller than symbol. Exposure to DHEA resulted in a reduced cell number compared to controls after 72 hours in 12.5  $\mu$ M, 48 hours in 25 or 50  $\mu$ M, and 24 hours in 200  $\mu$ M DHEA, indicating that DHEA produced a time- and dose-dependent inhibition of growth.

**Example 41: DHEA Effect on Cell Cycle**

To examine the effects of DHEA on cell cycle distribution, HT-29 SF cells were plated ( $10^5$  cells/60 mm dish), and 48 hours later treated with 0, 25, 50, or 200  $\mu$ M DHEA. FIG. 2 illustrates the effects of DHEA on cell cycle distribution in HT-29 SF cells. After 24, 48, and 72 hours, cells were harvested, fixed in ethanol, and stained with propidium iodide, and the DNA content/cell was determined by flow cytometric analysis. The percentage of cells in G<sub>1</sub>, S, and G<sub>2</sub>M phases was calculated using the Cellfit cell cycle analysis program. S phase is marked by a quadrangle for clarity. Representative histograms from duplicate determinations are shown. The experiment was repeated three times.

The cell cycle distribution in cultures treated with 25 or 50  $\mu$ M DHEA was unchanged after the initial 24 hours. However, as the time of exposure to DHEA increased, the proportion of cells in S phase progressively decreased, and the percentage of cells in G<sub>1</sub>, S and G<sub>2</sub>M phases was calculated using the Cellfit cell cycle analysis program. S phase is marked by a quadrangle for clarity. Representative histograms from duplicate determinations are shown. The experiment was repeated three times.

The cell cycle distribution in cultures treated with 25 or 50  $\mu$ M DHEA was unchanged after the initial 24 hours. However, as the time of exposure to DHEA increased, the proportion of cells in S phase progressively decreased and the percentage of cells in G<sub>1</sub> phase was increased after 72 hours. A transient increase in G<sub>2</sub>M phase cells was apparent after 48 hours. Exposure to 200  $\mu$ M DHEA produced a similar but more rapid increase in the percentage of cells in G<sub>1</sub> and a decreased proportion of cells in S phase after 24 hours, which continued through the treatment.

This indicates that DHEA produced a G<sub>1</sub> block in HT-29 SF cells in a time-and dose-dependent manner.

**Example 42: Reversal of DHEA-mediated Effect on Growth & Cell Cycle**

Reversal of DHEA-mediated Growth Inhibition. Cells were plated as above, and after 2 days received either 0 or 25  $\mu$ M DHEA-containing medium supplemented with mevalonic acid ("MVA"; 2 mM) squalene ("SQ"; 80  $\mu$ M), cholesterol ("CH"; 15  $\mu$ g/ml), MVA plus CH, ribonucleosides ("RN"; uridine, cytidine, adenosine, and guanosine at final concentrations of 30  $\mu$ M each), deoxyribonucleosides ("DN"; thymidine, deoxycytidine, deoxyadenosine and deoxyguanosine at final concentrations of 20  $\mu$ M each). RN plus DN, or MVA plus CH plus RN, or medium that was not supplemented. All compounds were obtained from Sigma Chemical Co. (St. Louis, Mo.) Cholesterol was solubilized in ethanol immediately before use. RN and DN were used in maximal concentrations shown to have no effects on growth in the absence of DHEA.

Figure 3 illustrates the reversal of DHEA-induced growth inhibition in HT-29 SF cells. In A, the medium was supplemented with 2  $\mu$ M MVA, 80  $\mu$ M SQ, 15  $\mu$ g/ml CH, or MVA plus CH (MVA+CH) or was not supplemented (CON). In B, the medium was supplemented with a mixture of RN containing uridine, cytidine, adenosine, and guanosine in final concentrations of 30  $\mu$ M each; a mixture of DN containing thymidine, deoxycytidine, deoxyadenosine and deoxyguanosine in final concentrations of 20  $\mu$ M each; RN plus DN (RN+DN); or MVA plus CH plus RN (MVA+CH+RN). Cell numbers were assessed before and after 48 hours of treatment, and culture growth was calculated as the increase in cell number during the 48 hour treatment period. Columns represent cell growth percentage of untreated controls; bars represent SEM. Increase in cell number in untreated controls was  $173,370 \pm 6518$ . Each data point represents quadruplicate dishes from four independent experiments. Statistical analysis was performed using Student's t test;  $\psi$   $p < 0.01$ ;  $\kappa$   $p < 0.001$ ; compared to treated controls. Note that supplements had little effect on culture growth in absence of DHEA.

Under these conditions, the DHEA-induced growth inhibition was partially overcome by addition of MVA as well as by addition of MVA plus CH. Addition of SQ or CH alone had no such effect. This suggest that the cytostatic activity of DHEA was in part mediated by depletion of endogenous mevalonate and subsequent inhibition of the biosynthesis of an early intermediate in the cholesterol pathway that is essential for cell growth. Furthermore, partial reconstitution of growth was found after addition of RN as well as after addition of RN plus DN but not after addition of DN, indicating that depletion of both mevalonate and nucleotide pools is involved in the growth-inhibitory action of DHEA. However, none of the reconstitution conditions including the combined addition of

MVA, CH, and RN completely overcame the inhibitory action of DHEA, suggesting either cytotoxic effects or possibly that additional biochemical pathways are involved.

**Example 43: Reversal of DHEA Effect on Cell Cycle**

HT-29 SF cells were treated with 25 FM DHEA in combination with a number of compounds, including MVA, CH, or RN, to test their ability to prevent the cell cycle-specific effects of DHEA. Cell cycle distribution was determined after 48 and 72 hours using flow cytometry.

Figure 4 illustrates reversal of DHEA-induced arrest in HT-29 SF cells. Cells were plated ( $10^5$  cells/60 mm dish) and 48 hours later treated with either 0 or 25 FM DHEA. The medium was supplemented with 2 FM MVA; 15 Fg/ml CH; a mixture of RN containing uridine, cytidine, adenosine, and guanosine in final concentrations of 30 FM; MVA plus CH (MVA+CH); or MVA plus CH plus RN (MVA+CH+RN) or was not supplemented. Cells were harvested after 48 or 72 hours, fixed in ethanol, and stained with propidium iodide, and the DNA content per cell was determined by flow cytometric analysis. The percentage of cells in G<sub>1</sub>, S, and G<sub>2</sub>M phases were calculated using the Cellfit cell cycle profile analysis program. S phase is marked by a quadrangle for clarity. Representative histograms from duplicative determinations are shown. The experiment was repeated two times. Note that supplements had little effect on cell cycle progression in the absence of DHEA.

With increasing exposure time, DHEA progressively reduced the proportion of cells in S phase. While inclusion of MVA partially prevented this effect in the initial 48 hours but not after 72 hours, the addition of MVA plus CH was also able to partially prevent S phase depletion at 72 hours, suggesting a requirement of both MVA and CH for cell progression during prolonged exposure. The addition of MVA, CH, and RN was apparently most effective at reconstitution but still did not restore the percentage of S phase cells to the value seen in untreated control cultures. CH or RN alone had very little effect at 48 hours and no effect at 72 hours. Morphologically, cells responded to DHEA by acquiring a rounded shape, which was prevented only by the addition of MVA to the culture medium (data not shown). Some of the DNA histograms after 72 hours DHEA exposure in FIG.4 also show the presence of a subpopulation of cells possessing apparently reduced DNA content. Since the HT-29 cell line is known to carry populations of cells containing varying numbers of chromosomes (68-72; ATCC), this may represent a subset of cells that have segregated carrying fewer chromosomes.

**Example 44: Conclusions**

The examples above provide evidence that in vitro exposure of HT-29 SF human colonic adenocarcinoma cells to concentrations of DHEA known to deplete endogenous mevalonate results in growth inhibition and G<sub>1</sub> arrest and that addition of MVA to the culture medium in part prevents these effects. DHEA produced effects upon protein isoprenylation which were in many respects similar to those observed for specific 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors such as lovastatin and compactin. Unlike direct inhibitors of mevalonate biosynthesis, however, DHEA mediates its effects upon cell cycle progression and cell growth in a pleiotropic manner involving ribo- and deoxyribonucleotide biosynthesis and possibly other factors as well.

The foregoing examples are illustrative of the present invention, but should not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

**Example 45: Effect of CoQs & an EA on In Vitro NADPH Levels**

Glucose-6-Phosphate Dehydrogenase (G6PD) is an important enzyme that is widespread in mammals, and is involved in the conversion of NADP to NADPH, thereby increasing NADPH levels. An inhibition of the G6PD enzyme, thus, will be expected to result in a reduction of cellular NADPH levels, which event, in turn, will be expected to inhibit pathways that are heavily dependent on NADPH. One such pathway, the so-called One-Carbon-Pool pathway, also known as the Folate Pathway, is directly involved in the production of adenosine by addition of the C<sub>2</sub> and C<sub>8</sub> carbon atoms of the purine ring. Consequently, the inhibition of this pathway will lead to adenosine depletion.

The present invention is broadly applicable to dehydroepiandrosterones (DHEAs) and Ubiquinones (CoQs). The description of the pathways involved in the present invention are described in the Background section. The present experiment was designed to show that one DHEA and two CoQs inhibit NADPH levels. DHEA, an dehydroepiandrosterone, has already been shown to decrease levels of adenosine in various tissues. See, Examples 1 and 2 above. The fact that two CoQs are shown to lower NADPH levels to a similar extent as a dehydroepiandrosterone, let alone to a similar extent ensures that the NADPH reduction caused by the CoQs will

also result in lower cellular adenosine levels or in adenosine cell depletion. Thus, in accordance with the invention, both dehydroepiandrosterones and Ubiquinones decrease levels of adenosine and, therefore, are useful as medicaments for use in the treatment of diseases where a decrease of adenosine levels or its depletion is desirable, including respiratory diseases such as asthma, bronchoconstriction, lung inflammation and allergies and the like.

- 5 Both Ubiquinones and DHEA inhibit NADPH levels in a statistically significant manner, when compared to a control. Moreover, the Ubiquinone inhibits NADPH levels to a similar extent as DHEA. The present invention is broadly applicable to the use of dehydroepiandrosterones (DHEAs) and Ubiquinones (CoQs) to the treatment of respiratory and lung diseases, and other diseases associated with varying levels of adenosine, adenosine hypersensitivity, asthma, bronchoconstriction, and/or lung inflammation and allergies. The DHEA and Ubiquinones  
10 employed in the present experiments are equivalent to those described and exemplified above.

#### **Enzymatic assay of purified G6PDH**

The reaction mixture contained 50mM glycyl glycine buffer, pH 7.4, 2 mM D-glucose-6-phosphate, 0.67 mM Beta-NADP, 10 mM MgCl<sub>2</sub> and 0.0125 units of G6PDH in a final volume of 3.0 ml. All experiments were repeated 4 times.

- 15 The control group contained 3 samples that were added no DHEA or ubiquinone. The experimental group contained a similar number of samples (3) for each concentration of DHEA or ubiquinone. One group was added DHEA (in triplicate) at different concentrations. A second group was added different concentrations of a CoQ of long side chain (in triplicate), and a third group received a CoQ of short side chain (in triplicate), both at various doses in the  $\mu$ M range.

- 20 The reaction was started by addition of the enzyme, and the increase in absorbance at 340 nm was measured for 5 minutes. Each data point was conducted in triplicate, and the full experiment was repeated 4 times.

- Both DHEA and the ubiquinones inhibited the enzyme activity in a statistically significant manner when compared to controls. DHEA was found to inhibit by 72% in vitro the activity of purified G6PDH when compared to control. Both ubiquinones inhibited the activity of purified G6PDH in vitro by an amount that was not  
25 statistically significantly different from that of DHEA. Both DHEA and the ubiquinones inhibited the enzyme in a statistically significant manner when compared to controls. Both long chain and short chain CoQs were found to be effective inhibitors of G6PDH.

- The above results clearly indicate that CoQ reduced cellular levels of NADPH to an extent similar to DHEA and consequently cellular adenosine levels, and has a therapeutic effect on diseases and conditions associated with them. The present results show that CoQs have a therapeutic effect similar to that of  
30 dehydroepiandrosterones. The pathways involved in the present invention, as described above, show the criticality of the results reported here, showing that a dehydroepiandrosterone (DHEA) and tow ubiquinones inhibit NADPH levels in a statistically significant manner. The same dehydroepiandrosterone (DHEA) was shown in Examples 1 and 2 to decrease levels of adenosine in various tissues. The two different ubiquinones employed lowered NADPH  
35 levels to a similar extent as DHEA. The NADPH reduction caused by the ubiquinones will, in the case of DHEA, result in lower cellular adenosine levels or adenosine depletion. Thus, in accordance with the invention, both dehydroepiandrosterones and ubiquinones decrease levels of adenosine and are, therefore, useful in the therapy of diseases and conditions where a decrease of adenosine levels or its depletion are desirable, including respiratory and airway diseases such as asthma, bronchoconstriction, lung inflammation and allergies, and the like.

- 40 In Examples 46 to 51, micronized anti-sense oligo targeting the adenosine A<sub>1</sub> receptor (EPI 2010) and micronized salmeterol (as the hydroxynaphthoate) are added in the proportions given below either dry or after predispersal in a small quantity of stabilizer, disodium dioctylsulphosuccinate, lecithin, oleic acid or sorbitan solvent to a suspension vessel containing the main bulk of the solvent. The resulting suspension is further dispersed by an appropriate mixing system using, for example, a high shear blender, ultrasonics or a microfluidiser until an ultrafine  
45 dispersion is created. The suspension is then continuously recirculated to suitable filling equipment designed for cold fill or pressure filling of solvent. The suspension may be also prepared in a suitable chilled solution of stabilizer, in solvent.

#### **Example 46: Metered Dose Inhaler**

Active Ingredient	Target per Actuation
DHEA	200 mg

EPI 2010	1 mg
Stabilizer	5.0 µg
Solvent (1)	23.70 mg
Solvent (2)	61.25 mg

**Example 47: Metered Dose Inhaler**

Active Ingredient	Target per Actuation
DHEA-S	200 mg
EPI 2010	5 mg
Stabilizer	7.5 µg
Solvent (1)	23.67 mg
Solvent (2)	61.25 mg

**Example 48: Metered Dose Inhaler**

Active Ingredient	Target per Actuation
Ubiquinone (CoQ10)	200 mg
EPI 2010	30 mg
Stabilizer	25.0 µg
Solvent (1)	23.45 mg
Solvent (2)	61.25 mg

5

**Example 49: Metered Dose Inhaler**

Active Ingredient	Target per Actuation
DHEA	600 mg µg
EPI 2010	1.0 mg
Stabilizer	15.0 µg
Solvent (1)	23.56 mg
Solvent (2)	61.25 mg

**Example 50: Metered Dose Inhaler**

Active Ingredient	Target per Actuation
DHEA-S	600 mg
EPI 2010	5.0 mg
Stabilizer	15.0 µg
Solvent (1)	23.56 mg
Solvent (2)	61.25 mg

10 **Example 51: Metered Dose Inhaler**

Active Ingredient	Target per Actuation
Ubiquinone	600 mg
EPI 2010	30.0 mg
Stabilizer	25.0 µg
Solvent (1)	23.43 mg
Solvent (2)	61.25 mg

In the following Examples 43 to 48, the active ingredients are micronized and bulk blended with lactose in the proportions given above. The blend is filled into hard gelatin capsules or cartridges or into specifically constructed double foil blister packs (Rotadisks blister packs, Glaxo® to be administered by an inhaler such as the Rotahaler inhaler (Glaxo®) or in the case of the blister packs with the Diskhaler inhaler (Glaxo®).

15

**Example 52: Metered Dose Dry Powder Formulation**

Active Ingredient	/cartridge or blister
DHEA	1 mg
EPI 2010	0.05 mg
Lactose Ph. Eur.	12.5 or 25.0 mg

**Example 53: Metered Dose Dry Powder Formulation**

Active Ingredient	/cartridge or blister
DHEA-S	1 mg
EPI 2010	0.1 mg
Lactose Ph. Eur.	12.5 or 25.0 mg

**Example 54: Metered Dose Dry Powder Formulation**

Active Ingredient	/cartridge or blister
Ubiquinone	1 mg
EPI 2010	0.15 mg
Lactose Ph. Eur.	12.5 or 25.0 mg

**Example 55: Metered Dose Dry Powder Formulation**

Active Ingredient	/cartridge or blister
DHEA	1 mg
EPI 2010	0.01 mg
Lactose Ph. Eur.	12.5 or 25.0 mg

**Example 56: Metered Dose Dry Powder Formulation**

Active Ingredient	/cartridge or blister
DHEA-S	1 mg
EPI 2010	0.05 mg
Lactose Ph. Eur.	12.5 or 25.0 mg

**Example 57: Metered Dose Dry Powder Formulation**

Active Ingredient	/cartridge or blister
Ubiquinone	1 mg
EPI 2010	0.1 mg
Lactose Ph. Eur.	12.5 or 25.0 mg

**Example 58: Metered Dose Inhaler Formulation (1)**

Standard 12.5 ml MDI (metered dose inhaler) cans (Presspart Inc., Cary N.C.) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1  $\mu$ m and approximately 20  $\mu$ m. These cans are then purged of air the valves crimped in place, and a suspension of about 68 mg of micronised beclomethasone dipropionate monohydrate and 1 mg of oligonucleotide in about 6.1 mg water and about 18.2 g P134a is filled through the valve.

**Example 59: Metered Dose Inhaler Formulation (2)**

Standard 12.5 ml MDI cans (Presspart Inc., Cary N.C.) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1  $\mu$ m and approximately 20  $\mu$ m. These cans are then purged of air the valves crimped in place, and about 50 mg of dehydroepiandrosterone, 1 mg of micronised oligonucleotide and 50 mg of Coenzyme Q10 in about 182 mg ethanol and about 18.2 g P134a is filled through the valve.

**Example 60: Metered Dose Inhaler Formulation (3)**

Standard 12.5 ml MDI cans (Presspart Inc., Cary N.C.) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1  $\mu\text{m}$  and approximately 20  $\mu\text{m}$ . These cans are then purged of air, the valves crimped in place, and a suspension of about 41.0 mg, 21.0 mg, 8.8 mg or 4.4 mg of micronised fluticasone propionate and 2 mg of micronised oligonucleotide in about 12 g P134a is filled through the valve.

**Example 61: Metered Dose Inhaler Formulation (4)**

Standard 12.5 ml MDI cans (Presspart Inc., Cary N.C.) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1  $\mu\text{m}$  and approximately 20  $\mu\text{m}$ . These cans are then purged of air, the valves crimped in place, and a suspension of about 8.8 mg, 22 mg or 44 mg of micronised fluticasone propionate with about 6.4 mg of micronised salmeterol xinafoate and 1 mg of micronised oligonucleotide in about 12 g P134a is filled through the valve.

**Example 62: Metered Dose Inhaler Formulation (5)**

Standard 12.5 ml MDI cans (Presspart Inc., Cary N.C.) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1  $\mu\text{m}$  and approximately 20  $\mu\text{m}$ . These cans are then purged of air the valves crimped in place, and a suspension of about 50mg of micronised dehydroepiandrosterone with about 6.4 mg of micronised salmeterol xinafoate and 2 mg of micronised oligonucleotide in about 12 g P134a is filled through the valve.

**Example 63: Metered Dose Inhaler Formulation (6)**

Standard 12.5 ml MDI cans (Presspart Inc., Cary N.C.) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1  $\mu\text{m}$  and approximately 20  $\mu\text{m}$ . These cans are then purged of air, the valves crimped in place, and a suspension of about 50 mg of micronised dehydroepiandrosterone sulfate and 2 mg of micronised oligonucleotide in about 12 g P134a is filled through the valve.

**Example 64: Effect of CoQs & an EA on In Vitro NADPH Levels**

Glucose-6-Phosphate Dehydrogenase (G6PD) is an important enzyme that is widespread in mammals, and is involved in the conversion of NADP to NADPH, thereby increasing NADPH levels. An inhibition of the G6PD enzyme, thus, will be expected to result in a reduction of cellular NADPH levels, which event, in turn, will be expected to inhibit pathways that are heavily dependent on NADPH. One such pathway, the so-called One-Carbon-Pool pathway, also known as the Folate Pathway, is directly involved in the production of adenosine by addition of the C<sub>2</sub> and C<sub>8</sub> carbon atoms of the purine ring. Consequently, the inhibition of this pathway will lead to adenosine depletion.

The present invention is broadly applicable to Epiandrosterones (EAs) and Ubiquinones (CoQs). The description of the pathways involved in the present invention are described in the Background section. The present experiment was designed to show that one EA and two CoQs inhibit NADPH levels. DHEA, an Epiandrosterone, has already been shown to decrease levels of adenosine in various tissues. See, Examples 1 and 2 above. The fact that two CoQs are shown to lower NADPH levels to a similar extent as an Epiandrosterone, let alone to a similar extent ensures that the NADPH reduction caused by the CoQs will also result in lower cellular adenosine levels or in adenosine cell depletion. Thus, in accordance with the invention, both Epiandrosterones and Ubiquinones decrease levels of adenosine and, therefore, are useful as medicaments for use in the treatment of diseases where a decrease of adenosine levels or its depletion is desirable, including respiratory diseases such as asthma, bronchoconstriction, lung inflammation and allergies and the like. Both Ubiquinones and DHEA inhibit NADPH levels in a statistically significant manner, when compared to a control. Moreover, the Ubiquinone inhibits NADPH levels to a similar extent as DHEA. The present invention is broadly applicable to the use of Epiandrosterones (EAs) and Ubiquinones (CoQs) to the treatment of respiratory and lung diseases, and other diseases associated with varying levels of adenosine, adenosine hypersensitivity, asthma, bronchoconstriction, and/or lung inflammation and allergies. The



DHEA and Ubiquinones employed in the present experiments are equivalent to those described and exemplified above.

**Enzymatic assay of purified G6PDH**

5 The reaction mixture contained 50mM glycyl glycine buffer, pH 7.4, 2 mM D-glucose-6-phosphate, 0.67 mM Beta-NADP, 10 mM MgCL<sub>2</sub> and 0.0125 units of G6PDH in a final volume of 3.0 ml. All experiments were repeated 4 times.

10 The control group contained 3 samples that were added no DHEA or Ubiquinone. The experimental group contained a similar number of samples (3) for each concentration of DHEA or Ubiquinone. One group was added DHEA (in triplicate) at different concentrations. A second group was added different concentrations of a CoQ of long side chain (in triplicate), and a third group received a CoQ of short side chain (in triplicate), both at various doses in the  $\mu$ M range.

The reaction was started by addition of the enzyme, and the increase in absorbance at 340 nm was measured for 5 minutes. Each data point was conducted in triplicate, and the full experiment was repeated 4 times.

15 Both DHEA and the Ubiquinones inhibited the enzyme activity in a statistically significant manner when compared to controls. DHEA was found to inhibit by 72% in vitro the activity of purified G6PDH when compared to control. Both Ubiquinones inhibited the activity of purified G6PDH in vitro by an amount that was not statistically significantly different from that of DHEA. Both DHEA and the Ubiquinones inhibited the enzyme in a statistically significant manner when compared to controls. Both long chain and short chain CoQs were found to be effective inhibitors of G6PDH.

20 The above results clearly indicate that CoQ reduced cellular levels of NADPH to an extent similar to DHEA and consequently cellular adenosine levels, and has a therapeutic effect on diseases and conditions associated with them. The present results show that CoQs have a therapeutic effect similar to that of epiandrosterones. The pathways involved in the present invention, as described above, show the criticality of the results reported here, showing that an Epiandrosterone (DHEA) and two Ubiquinones inhibit NADPH levels in a statistically significant manner. The same epiandrosterone (DHEA) was shown in Examples 1 and 2 to decrease levels of adenosine in various tissues. The two different Ubiquinones employed lowered NADPH levels to a similar extent as DHEA. The NADPH reduction caused by the Ubiquinones will, in the case of DHEA, result in lower cellular adenosine levels or adenosine depletion. Thus, in accordance with the invention, both Epiandrosterones and Ubiquinones decrease levels of adenosine and are, therefore, useful in the therapy of diseases and conditions where a decrease of adenosine levels or its depletion are desirable, including respiratory and airway diseases such as asthma, bronchoconstriction, lung inflammation and allergies, and the like.

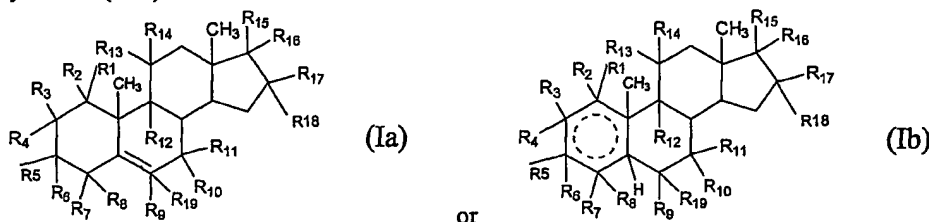
25 These are clearly superior results, which could not have been expected based on the knowledge of the art at the time of this invention. The experimental data and results provided are clearly enabling of the effect of ubiquinones on adenosine cellular levels and, therefore, on its therapeutic affect on diseases and conditions associated with them, as described and claimed in this patent.

35 The foregoing examples are illustrative of the present invention, and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

**WHAT IS CLAIMED AS NOVEL & UNOBVIOUS****IN UNITED STATES LETTERS PATENT IS:**

1. A pharmaceutical composition, comprising a pharmaceutically or veterinarily acceptable carrier or diluent, and prophylactic or therapeutic amounts of a first and second active agents;

the first active agent comprising an oligonucleotide(s) (oligo(s)) that is anti-sense to the initiation codon, the coding region, the 5'-end or the 3'-end genomic flanking regions, the 5' and 3' intron-exon junctions, or regions within 2 to 10 nucleotides of the junctions of one or more gene(s) encoding or to regulatory sequence(s) associated with one or more target polypeptide(s) associated with lung and/or nasal airway dysfunction, or anti-sense to the corresponding mRNA; or combinations or mixtures of the oligo(s); and the second active agent comprising an anti-inflammatory steroid (AJS) of chemical formula



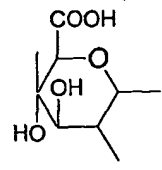
wherein  $R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9, R_{10}, R_{12}, R_{13}, R_{14}$  and  $R_{19}$  are independently H, OR, halogen,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene,  $(C_1-C_{10})$  alkyne,  $(C_1-C_{10})$  alkoxy, or two or more of  $R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_9, R_{10}, R_{12}, R_{13}, R_{14}$  and  $R_{19}$  can be linked by combination of the atoms of C, O, N, S, P and Si to form a 3 to 15 member ring(s), in the  $\alpha$ - and/or  $\beta$ - configuration;

$R_5, R_6, R_{10}$ , and  $R_{11}$  are independently OH, SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane,  $-OSO_2R_{20}$ ,  $-OPOR_{20}R_{21}$ ,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene,  $(C_1-C_{10})$  alkyne or  $OR_{23}$ ,  $-SO_2O-CH_2CHCH_2OCOR_{25}$

wherein,  $R_{23}$  is hydrogen or  $SO_2OM$ , wherein M is selected from H, Na, sulfatide;



phosphatide  $OCOR_{24}$ , wherein  $R_{24}$  and  $R_{25}$ , which may be the same or different, are straight or branched  $(C_1-C_{20})$  alkyl,  $(C_1-C_{20})$  alkene,  $(C_1-C_{20})$  alkyne, sugar, polyethyleneglycol (PEG) or glucuronide



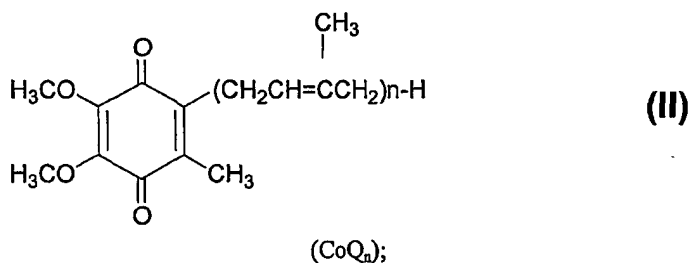
$R_5$  and  $R_6$  taken together are =O;

$R_{10}$  and  $R_{11}$  taken together are =O;

$R_{15}$  is (1) H, halogen,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene,  $(C_1-C_{10})$  alkyne, or  $(C_1-C_{10})$  alkoxy when  $R_{16}$  is  $-C(O)OR_{22}$ , (2) H, halogen, OH,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene or  $(C_1-C_{10})$  alkyne, when  $R_{16}$  is halogen, OH,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene or  $(C_1-C_{10})$  alkyne, (3) H, halogen,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkenyl,  $(C_1-C_{10})$  alkynyl, formyl,  $(C_1-C_{10})$  alkanoyl or epoxy when  $R_{16}$  is OH, (4) OR, SR, SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane,  $-OSO_2R_{20}$  or  $-OPOR_{20}R_{21}$  when  $R_{16}$  is H, or  $R_{15}$  and  $R_{16}$  taken together are =O;

$R_{17}$  and  $R_{18}$  are independently (1) H, -OH, halogen,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene,  $(C_1-C_{10})$  alkyne or  $-(C_1-C_{10})$  alkoxy when  $R_6$  is H OR, halogen,  $(C_1-C_{10})$  alkyl or  $-C(O)OR_{22}$ , (2) H,  $(C_1-C_{10})$  alkyl, amino,  $(C_1-C_{10})$  alkene, amino,  $(C_1-C_{10})$  alkyne, amino,  $((C_1-C_{10})$  alkyl), amino- $(C_1-C_{10})$  alkyl,  $((C_1-C_{10})$  alkene), amino- $(C_1-C_{10})$  alkyl,  $((C_1-C_{10})$  alkyne), amino- $(C_1-C_{10})$  alkyl,  $((C_1-C_{10})$  alkyl), amino- $(C_1-C_{10})$  alkene,  $((C_1-C_{10})$  alkene), amino- $(C_1-C_{10})$  alkene,  $((C_1-C_{10})$  alkyne), amino- $(C_1-C_{10})$  alkene,  $((C_1-C_{10})$  alkyl), amino- $(C_1-C_{10})$  alkyne,  $((C_1-C_{10})$  alkene), amino- $(C_1-C_{10})$  alkyne,  $((C_1-C_{10})$  alkyne), amino- $(C_1-C_{10})$  alkyne,  $(C_1-C_{10})$  alkoxy, hydroxy -  $(C_1-C_{10})$  alkyl; hydroxy -  $(C_1-C_{10})$  alkene, hydroxy -  $(C_1-C_{10})$  alkyne,  $(C_1-C_{10})$  alkoxy -  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkoxy -  $(C_1-C_{10})$  alkene,  $(C_1-C_{10})$  alkoxy -  $(C_1-C_{10})$  alkyne,  $(\text{halogen})_m$   $(C_1-C_{10})$  alkyl,  $(\text{halogen})_m$   $(C_1-C_{10})$  alkene,  $(\text{halogen})_m$   $(C_1-C_{10})$  alkyne,  $(C_1-C_{10})$  alkanoyl, formyl,  $(C_1-C_{10})$  carbalkoxy or  $(C_1-C_{10})$  alkanoyloxy when  $R_{15}$  and  $R_{16}$  taken together are =O, (3)  $R_{17}$  and  $R_{18}$  taken together are =O; (4)  $R_{17}$  and  $R_{18}$  taken together with the carbon to which they are attached form a 3-6 member ring containing 0 or 1 oxygen atom; or (5)  $R_{15}$  and  $R_{17}$  taken together with the carbons to which they are attached form an epoxide ring;  $R_{20}$  and  $R_{21}$  are independently OH, pharmaceutically acceptable ester or pharmaceutically acceptable ether;  $R_{22}$  is H,  $(\text{halogen})_m$   $(C_1-C_{10})$  alkyl,  $(\text{halogen})_m$   $(C_1-C_{10})$  alkene,  $(\text{halogen})_m$   $(C_1-C_{10})$  alkyne,  $(C_1-C_{10})$  alkyl,  $(C_1-C_{10})$  alkene or  $(C_1-C_{10})$  alkyne; n is 0, 1 or 2; and m is 1, 2 or 3, ; or pharmaceutically or veterinarily acceptable salts thereof; and/or

a ubiquinone of the chemical formula



wherein  $n=1$  to 12, or pharmaceutically or veterinarily acceptable salts thereof; the first and second agents being present in amounts effective for reducing or depleting levels of, or reducing sensitivity to, adenosine, reducing levels of adenosine receptors, producing bronchodilation, increasing levels of ubiquinone or lung surfactant in a subject's tissue (s), or treating bronchoconstriction, lung inflammation or lung allergies or a respiratory or lung disease or condition.

2. The composition of claim 1, wherein the oligo contains up to about 15% A.
3. The composition of claim 1, wherein the oligo(s) of the first active agent is (are) anti-sense to the initiation codon, the coding region, the 5'-end or the 3'-end genomic flanking regions, the 5' or 3' intron-exon junctions, and regions within 2 to 10 nucleotides of the junctions of at least one oncogene(s) or a gene(s) encoding, or regulating expression of, a target polypeptide(s) associated with lung and/or nasal airway dysfunction or cancer, is (are) anti-sense to the corresponding mRNA(s). Multiple target anti-sense oligo(s) (MTAs) or combinations thereof; the polypeptides comprising peptide factors and transmitters, antibodies, cytokines or chemokines, enzymes, binding proteins, adhesion molecules, their receptors, or malignancy associated proteins.
4. The composition of claim 3, wherein the oligo(s) is (are) anti-sense to the initiation codon, the coding region, the 5'-end or the 3'-end genomic flanking regions, the 5' or 3' intron-exon junctions, or regions within 2 to 10 nucleotides of the junctions of at least one oncogene(s) or a gene(s) encoding, or regulating expression of, a target polypeptide(s) associated with lung and/or nasal airway dysfunction or is (are) anti-sense to the oncogene mRNA, or the corresponding mRNA; or MTAs or combinations thereof; wherein the polypeptides comprise of transcription factors, stimulating or activating peptide factors, cytokines, cytokine receptors, chemokines, chemokine receptors, adenosine receptors, bradykinin receptors, endogenously produced specific or non-specific enzymes, immunoglobulins or antibodies, antibody receptors, central nervous system (CNS) or peripheral nervous or non-nervous system receptors, CNS or peripheral nervous or non-nervous system peptide transmitters, adhesion molecules, defensins, growth factors, vasoactive peptides and receptors, binding proteins, or malignancy associated proteins.
5. The composition of claim 4, wherein the encoded polypeptide(s) comprise(s) one or more adenosine receptors  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$  or  $A_3$ , bradykinin receptors B1 or B2, NfκB Transcription Factor, Interleukin-8

Receptor (IL-8 R), Interleukin 5 Receptor (IL-5 R), Interleukin 4 Receptor (IL-4 R), Interleukin 3 Receptor (IL-3 R), Interleukin-1 $\beta$  (IL-1 $\beta$ ), Interleukin 1 $\beta$  Receptor (IL-1 $\beta$  R), Eotaxin, Tryptase, Major Basic Protein,  $\beta$ 2-adrenergic Receptor Kinase, Endothelin Receptor A, Endothelin Receptor B, Preproendothelin, Bradykinin B2 Receptor, IgE High Affinity Receptor, Interleukin 1 (IL-1), Interleukin 1 Receptor (IL-1 R), Interleukin 9 (IL-9), Interleukin-9 Receptor (IL-9 R), Interleukin 11 (IL-11), Interleukin-11 Receptor (IL-11 R), Inducible Nitric Oxide Synthase, Cyclo-oxygenase-1 (COX-1), Cyclo-oxygenase-2 (COX-2), Intracellular Adhesion Molecule 1 (ICAM-1) Vascular Cellular Adhesion Molecule (VCAM), Rantes, Endothelial Leukocyte Adhesion Molecule (ELAM-1), Monocyte Activating Factor, Neutrophil Chemotactic Factor, Neutrophil Elastase, Defensin 1, 2 and 3, Muscarinic Acetylcholine Receptors, Platelet Activating Factor, Tumor Necrosis Factor  $\alpha$ , 5-lipoxygenase, Phosphodiesterase IV, Substance P, Substance P Receptor, Histamine Receptor, Chymase, CCR-1 CC Chemokine Receptor, CCR-2 CC Chemokine Receptor, CCR-3 CC Chemokine Receptor, CCR-4 CC Chemokine Receptor, CCR-5 CC Chemokine Receptor, Prostanoid Receptors, GATA-3 Transcription Factor, Neutrophil Adherence Receptor, MAP Kinase, Interleukin-9 (IL-9), NFAT Transcription Factors, STAT 4, MIP-1 $\alpha$ , MCP-2, MCP-3, MCP-4, Cyclophilins, Phospholipase A2, Basic Fibroblast Growth Factor, Metalloproteinase, CSBP/p38 MAP Kinase, Tryptase Receptor, PDG2, Interleukin-3 (IL-3), Interleukin-1 $\beta$  (IL-1 $\beta$ ), Cyclosporin A-Binding Protein, FK5-Binding Protein,  $\alpha$ 4 $\beta$ 1 Selectin, Fibronectin,  $\alpha$ 4 $\beta$ 7 Selectin, Mad CAM-1, LFA-1 (CD11a/CD18), PECAM-1, LFA-1 Selectin, C3bi, PSGL-1, E-Selectin, P-Selectin, CD-34, L-Selectin, p150,95, Mac-1 (CD11b/CD18), Fucosyl transferase, VLA-4, CD-18/CD11a, CD11b/CD18, ICAM2 and ICAM3, C5a, CCR3 (Eotaxin Receptor), CCR1, CCR2, CCR4, CCR5, LTB-4, AP-1 Transcription Factor, Protein kinase C, Cysteinyl Leukotriene Receptor, Tachychinins Receptors (tach R), I $\kappa$ B Kinase 1 & 2, STAT 6, c-mas or NF-Interleukin-6 (NF-IL-6).

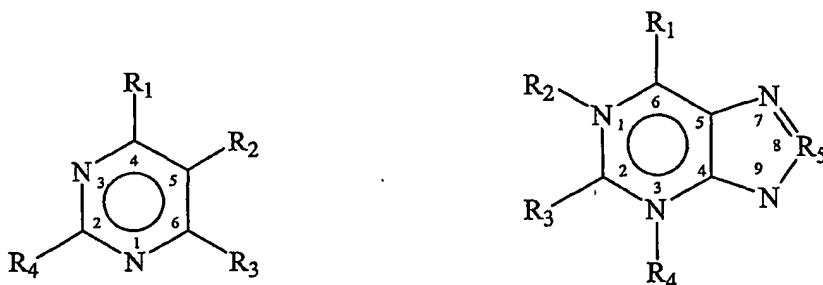
6. The composition of claim 4, wherein the encoded polypeptide(s) comprise(s) a H2A histone family member N, Tubulin, beta polypeptide, ELL gene (11-19 lysine-rich leukemia gene); 7-dehydrocholesterol reductase, ADP-ribosylation factor-like 7, Karyopherin alpha 2 (RAG cohort 1, importin alpha 1), EST (AI038433), EST (AI122689), EST (AI092623), ESTs (AI095492), ESTs (AI138216), ESTs (AI128305), ESTs (AI125228), ESTs (AI041482), ESTs (AI051839), Homo sapiens mRNA; cDNA DKFZp434A1716, ESTs (AI096522), ESTs (AI122807), ESTs (AI041212), EST (AI125651), Enolase 1, (alpha), EST (AI024215), EST (AI034360), Homo sapiens mRNA; cDNA DKFZp564H0764, Homo sapiens mRNA for KIAA1363 protein, partial cds, Potassium voltage-gated channel, shaker-related subfamily, beta member 2, ER-associated DNAJ; ER-associated Hsp40 co-chaperone; hDj9; ERj3, ESTs, Weakly similar to p38 protein [H.sapiens] (AA906703), CGI-142, ESTs (AA463249), Homo sapiens clone 25058 mRNA sequence ESTs (R49144), Squamous cell carcinoma antigen 1, ESTs (AA425700), Myosin X, ESTs (AA459692), Epithelial protein lost in neoplasm beta, CD44 antigen (homing function and Indian blood group system), Coagulation factor III (thromboplastin, tissue factor), ESTs (AA909635), Adducin 1 (alpha), 5' Nucleotidase (CD73), ESTs, moderately similar to semaphorin C [M.musculus] (AA293300), ESTs (AA278764), ESTs (AA678160), Calmodulin 2 (phosphorylase kinase, delta), ESTs (R42770), Chloride intracellular channel 1, High-mobility group (nonhistone chromosomal) protein 17, Ubiquitin carrier protein, Tubulin, alpha 1 (testis specific), Transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase), Sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican), Proteasome (prosome, macropain) 26S subunit, non-ATPase, 2, Tubulin, beta polypeptide, Filamin B, beta (actin-binding protein-278), Stanniocalcin, Low density lipoprotein receptor (familial hypercholesterolemia), Plectin 1, intermediate filament binding protein, 500kD, S100 calcium-binding protein A2, Immediate early response 3, Calpain, large polypeptide L2, Pleckstrin homology-like domain, family A, member 1, Melanoma adhesion molecule, CD44 antigen (homing function and Indian blood group system), Programmed cell death 5, Hexokinase 1, Vascular endothelial growth factor, Integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor), Calumenin, Syntaxin 11, Diphtheria toxin receptor (heparin-binding epidermal growth factor-like growth factor), Fn14 for type I transmembrane protein, Nef-associated factor 1, High-mobility group (nonhistone chromosomal) protein isoforms I and Y, Catechol-O-methyltransferase, C-terminal binding protein 1, Collagen, type XVII, alpha 1, ESTs (N58473), Farnesyl-diphosphate farnesyltransferase 1 RNA helicase-related protein, Interferon stimulated gene (20kD), Steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1), Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase), Laminin, alpha 3 (nicein (150kD), kalinin (165kD), BM600 (150kD), epilegrin), Collagen, type XVII, alpha 1, Keratin 18, Heparan sulfate (glucosamine) 3-O-sulfotransferase 1, Tubulin, alpha 2, Adenylyl cyclase-associated protein, Forkhead box D1, Cathepsin C, ESTs, Highly similar to AF151802\_1 CGI-44 protein [H.sapiens] (T74688), Ribonucleotide reductase

M2 polypeptide, Laminin, gamma 2 (nicein (100kD), kalinin (105kD), BM600 (100kD), Herlitz junctional epidermolysis bullosa)), Homo sapiens mRNA; cDNA DKFZp586P1622 (from clone DKFZp586P1622), ESTs, Weakly similar to /prediction (AA284245), or Lactate dehydrogenase A.

7. The composition of claim 1, wherein one or more As of the first active agent is(are) substituted by a universal base comprising a heteroaromatic base that binds to thymidine or uridine but has antagonist activity or less than about 0.3 of the adenosine agonist or antagonist activity at the adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> or A<sub>3</sub> receptors.

8. The composition of claim 7, wherein the heteroaromatic base(s) comprise(s) pyrimidines or purines, which may be substituted by O, halo, NH<sub>2</sub>, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, COOH, branched or fused primary or secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, all of which may be further substituted by O, halo, NH<sub>2</sub>, primary, secondary or tertiary amine, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, cycloalkyl, heterocycloalkyl or heteroaryl.

9. The composition of claim 7, wherein the purines are substituted at positions 1, 2, 3, 6, and/or 8, the pyrimidines are substituted at positions 2, 3, 4, 5 and/or 6, and the purines and pyrimidines have the chemical formula



pyrimidines

or

purines

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently H, alkyl, alkenyl or alkynyl and R<sup>3</sup> is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl, NH<sub>2</sub>-alkylamino-ketoxyalkyloxy-aryl, or mono or dialkylaminoalkyl-N-alkylamino-SO<sub>2</sub>aryl, and R<sub>4</sub> and R<sub>5</sub> are independently R<sub>1</sub> and together are R<sub>3</sub>, and the pyrimidines and purines optionally comprise theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline or xanthine.

10. The composition of claim 9, wherein the universal base of the first active agent comprises 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.

11. The composition of claim 1, wherein if present in the first active agent(s), one or more methylated cytosine(s) (<sup>m</sup>C) is(are) substituted for a C in or to form one or more CpG dinucleotide(s).

12. The composition of claim 1, wherein one or more mononucleotide(s) of the first active agent(s) is(are) linked or modified by one or more of methylphosphonate, 5'-N-carbamate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methylimino) (MMI), methoxymethyl (MOM), methoxyethyl (MOE), methyleneoxy (methylimino) (MOMI), 2'-O-methyl, phosphoramidate, or C-5 substituted residues.

13. The composition of claim 12, wherein one or more mononucleotide residue(s) of the first active agent(s) are linked by phosphorothioate residues.

14. The composition of claim 1, wherein the anti-sense oligo of the first active agent(s) comprise(s) about 7 to about 60 mononucleotides.

15. The composition of claim 1, wherein the anti-sense oligo of the first active agent(s) comprise(s) fragments 1, 3, 5, 7 and 8 to 2498 (SEQ ID NOS: 1 through 2498).

16. The composition of claim 1, wherein the anti-sense oligo of the first active agent(s) is(are) operatively linked to, or complexed with, a cell internalized or up-taken agent(s) or a cell targeting agent(s).

17. The composition of claim 15, wherein the cell internalized or up-taken agent comprises transferrin, asialoglycoprotein or streptavidin, and the cell targeting agent comprises a prokaryotic or eukaryotic vector or plasmid.

18. The composition of claim 1, wherein the oligo contains up to about 10% A.

19. The composition of claim 1, wherein the oligo(s) of the first active agent(s) is(are) hybridized to a ribonucleic acid or a deoxyribonucleic acid and delivered as a double stranded agent.

20. The composition of claim 1, wherein the carrier or diluent comprises a gaseous, liquid, or solid carrier or diluent, and the active agents are present in an amount of about 0.01 to about 99.99 w/w of the composition.

21. The composition of claim 20, further comprising an agent selected from other therapeutic agents, surfactants, flavoring or coloring agents, fillers, volatile oils, buffering agents, dispersants, RNA inactivating agents, anti-oxidants, flavoring agents, propellants or preservatives.

22. The composition of claim 21, wherein the other therapeutic or bioactive agent(s) is (are) selected from analgesics, pre-menstrual medications, menopausal agents, anti-aging agents, anti-anxiolytic agents, mood disorder agents, anti-depressants, anti-bipolar mood agents, anti-schizophrenic agents, anti-cancer agents, alkaloids, blood pressure controlling agents, muscle relaxants, steroids, soporific agents, anti-ischemic agents, anti-arrhythmic agents, contraceptives, vitamins, minerals, tranquilizers, neurotransmitter regulating agents, wound healing agents, anti-angiogenic agents, cytokines, growth factors, B-adrenergic receptor agonists, anti-metastatic agents, antacids, anti-histaminic agents, anti-bacterial agents, anti-viral agents, anti-gas agents, appetite suppressants, sun screens, emollients, skin temperature lowering products, radioactive phosphorescent or fluorescent contrast diagnostic or imaging agents, libido altering agents, bile acids, laxatives, anti-diarrheic agents, skin renewal agents, hair growth agents, analgesics, pre-menstrual medications, anti-menopausal agents, hormones, anti-aging agents, anti-anxiolytic agents, nociceptic agents, mood disorder agents, anti-depressants, anti-bipolar mood agents, anti-schizophrenic agents, anti-cancer agents, alkaloids, blood pressure controlling agents, other hormones, other anti-inflammatory agents, agents for treating arthritis, burns, wounds, chronic bronchitis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease such as Crohn's disease, ulcerative colitis, autoimmune disease, or lupus erythematosus, muscle relaxants, soporific agents, anti-ischemic agents, anti-arrhythmic agents, contraceptives, vitamins, minerals, tranquilizers, neurotransmitter regulating agents, wound and burn healing agents, anti-angiogenic agents, cytokines, growth factors, anti-metastatic agents, antacids, anti-histaminic agents, anti-bacterial agents, anti-viral agents, anti-gas agents, agents for reperfusion injury, counteracting appetite suppressants, sun screens, emollients, skin temperature lowering products, radioactive phosphorescent or fluorescent contrast diagnostic or imaging agents, libido altering agents, bile acids, laxatives, anti-diarrheic agents, skin renewal agents or hair growth agents.

23. The composition of claim 22, wherein the surfactant comprises surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant Protein E, di-saturated phosphatidyl choline (other than dipalmitoyl), dipalmitoyl phosphatidyl choline, phosphatidyl choline, phosphatidyl glycerol, phosphatidyl inositol, phosphatidyl ethanolamine, phosphatidyl serine; phosphatidic acid, ubiquinones, lysophosphatidyl ethanolamine, lysophosphatidyl choline, palmitoyl- lysophosphatidyl choline, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxy acetone, palmitate, cytidine diphosphate (CDP) diacyl glycerol, CDP choline, choline, choline phosphate; natural or artificial lamellar bodies as carrier surfactant vehicles, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic block copolymers of ethylene or propylene oxides, polyoxypropylene, monomeric or polymeric, polyoxyethylene, monomeric and polymeric, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100 or synthetic surfactants ALEC, Exosurf, Survan or Atovaquone.

24. The composition of claim 1, comprising one or more oligo(s), an anti-inflammatory steroid(s) of formula (Ia) or (Ib), a steroid, a surfactant, and a carrier or diluent for the oligo.

25. The composition of claim 1, wherein the second active agent comprises  $\text{CoQ}_n$ , wherein n is 1 to 10.

26. The composition of claim 1, wherein the second active agent comprises  $\text{CoQ}_n$ , wherein n is 6 to

10.

27. The composition of claim 1, wherein the second active agent comprises  $\text{CoQ}_n$ , wherein  $n$  is 10.
28. The composition of claim 1, wherein the second active agent comprises an anti-inflammatory steroid (AIS) of formula (Ia) selected from dehydroepiandrosterone, wherein  $R$  and  $R^1$  are H and the broken line represents a double bond, 16- $\alpha$  bromodehydroepiandrosterone wherein  $R$  is Br,  $R^1$  is H and the broken line represents a double bond, 16- $\alpha$ fluorodehydroepiandrosterone wherein  $R$  is F,  $R^1$  is H and the broken line represents a double bond, etiocholanolone, wherein  $R$  and  $R^1$  are each hydrogen and the broken line represents a single bond, dehydroepiandrosterone sulfate, wherein  $R$  is H,  $R^1$  is  $\text{SO}_2\text{OM}$  and  $M$  is a sulfatide group as defined above, and the broken line represents a double bond, the compound of formula (Ia),  $R$  is halogen selected from Br, Cl or F,  $R^1$  is H, and the broken line represents a double bond, 16- $\alpha$ -fluorodehydro-epiandrosterone, or pharmaceutically or veterinarily acceptable salts thereof.
29. The composition of claim 1, wherein the oligo(s) of the first agent contains up to about 5% A.
30. The composition of claim 1, wherein the oligo(s) of the first agent is A free.
31. The composition of claim 1, wherein the second active agent comprises an anti-inflammatory steroid (AIS) of formula (Ib), wherein  $R^{15}$  and  $R^{16}$  together are  $=\text{O}$ ;  $R^5$  is  $-\text{OH}$ ;  $R^5$  is  $-\text{OSO}_2\text{R}^{20}$ ;  $R^{15}$  and  $R^{20}$  together is H; or pharmaceutically or veterinarily acceptable salts thereof.
32. The composition of claim 1, wherein the second active agent comprises an AIS selected from budesonide, testosterone, progesterone, fluticasone, beclomethasone, prednisone, mometasone, estrogen, dexamethasone, hydrocortisone, triamcinolone, flunisolide, methylprednisolone prednisone, hydrocortisone, or analogues thereof.
33. The composition of claim 1, wherein the active agents are present in an amount of about 0.01 to about 99.99 w/w of the composition.
34. The composition of claim 1, wherein the second active agent comprises an anti-inflammatory steroid (AIS) selected from 21-acetoxypregnenolone (( $3\beta$ )-21-(acetyloxy)-3-hydroxypregn-5-en-20-one); alclometasone (( $7\alpha$ , 11 $\beta$ , 16 $\alpha$ )-7-Chloro-11, 17, 21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), or its 17,21-dipropionate form ( $\text{C}_{28}\text{H}_{37}\text{ClO}_7$ ); algestone ((16 $\alpha$ )-16,17-dihydroxypregn-4-ene-3,20-dione), its cyclic acetal with acetone form ( $\text{C}_{24}\text{H}_{34}\text{O}_4$ ), or its 16 $\alpha$ -methyl ether form ( $\text{C}_{22}\text{H}_{32}\text{O}_4$ ); amcinonide ((11 $\beta$ , 16 $\alpha$ )-21-(acetyloxy)-16,17-[cyclopentylidenebis(oxy)]-9-fluoro-11-hydroxypregna-1,4-di-ene-3,20-dione); beclomethasone ((11 $\beta$ ,16 $\beta$ )-9-chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), its dipropionate form ( $\text{C}_{28}\text{H}_{37}\text{ClO}_7$ ), or its monopropionate form; betamethasone ((11 $\beta$ , 16 $\beta$ )-9-fluoro-11, 17, 21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $\text{C}_{24}\text{H}_{31}\text{FO}_6$ ), its 21-adamantoate form ( $\text{C}_{33}\text{H}_{43}\text{FO}_6$ ), its 17-benzoate form ( $\text{C}_{29}\text{H}_{33}\text{FO}_6$ ), its 17, 21-dipropionate form ( $\text{C}_{28}\text{H}_{37}\text{FO}_7$ ), its 17-valerate form ( $\text{C}_{27}\text{H}_{37}\text{FO}_6$ ), or its 21-phosphate disodium salt form ( $\text{C}_{22}\text{H}_{28}\text{FNa}_2\text{O}_8\text{P}$ ); budesonide ((11 $\beta$ , 16 $\alpha$ )-16,17-[butylidenebis(oxy)]-11, 21-dihydropregna-1,4-diene-3,20-dione); chloroprednisone ((6 $\alpha$ )-chloro-17,21-dihydroxypregna-1,4-diene-3,11,20-trione), or its 21-acetate form ( $\text{C}_{23}\text{H}_{27}\text{ClO}_6$ ); ciclesonide; clobetasol ((11 $\beta$ ,16 $\beta$ )-21-chloro-9-fluoro-11,17-dihydroxy-16-methylpregna-1,4-diene-3,20-dione), or its 17-propionate form ( $\text{C}_{25}\text{H}_{33}\text{ClFO}_5$ ); clobetasone ((16 $\beta$ )-21-chloro-9-fluoro-17-hydroxy-16-methylpregna-1,4-diene-3,11,20-trione), or its 17-butyrate form ( $\text{C}_{26}\text{H}_{32}\text{ClFO}_5$ ); clocortolone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-9-chloro-6-fluoro-11,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $\text{C}_{24}\text{H}_{30}\text{ClFO}_5$ ), or its 21-pivalate form ( $\text{C}_{27}\text{H}_{36}\text{ClFO}_5$ ); cloprednol ((11 $\beta$ )-6-chloro-11,17,21-trihydroxypregna-1,4,6-triene-3,20-dione); coroxon (phosphoric acid 3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl diethyl ester); cortisone (17,21-dihydroxypregn-4-ene-3,11,20-trione), its 21-acetate form ( $\text{C}_{23}\text{H}_{30}\text{O}_6$ ), or its 21-cyclopentanepropionate form ( $\text{C}_{29}\text{H}_{40}\text{O}_6$ ); cortivazol ((11 $\beta$ ,16 $\alpha$ )-21-(acetyloxy)-11,17-dihydroxy-6,16-dimethyl-2'-phenyl-2'-H-pregna-2,4,6-trieno[3,2-c]pyrazol-20-one); deflazacort ((11 $\beta$ ,16 $\beta$ )-21-(acetyloxy)-11-hydroxy-2'-methyl-5'-H-pregna-1,4-dieno[17,16-d]oxazole-3,20-dione); desonide ((11 $\beta$ ,16 $\alpha$ )-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione); desoximetasone ((11 $\beta$ ,16 $\alpha$ )-9-fluoro-11, 21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione); dexamethasone ((11 $\beta$ ,16 $\alpha$ )-9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $\text{C}_{24}\text{H}_{31}\text{FO}_6$ ), its 21-(3,3-dimethylbutyrate) form ( $\text{C}_{28}\text{H}_{39}\text{FO}_6$ ; Chemerda et al., US Patent No. 2,939,873), its 21-diethylaminoacetate form ( $\text{C}_{28}\text{H}_{41}\text{FNO}_6$ ), its 21-isonicotinate form ( $\text{C}_{28}\text{H}_{41}\text{FNO}_6$ ), its 17,21-dipropionate form ( $\text{C}_{28}\text{H}_{37}\text{FNO}_6$ ), or its 21-palmitate form ( $\text{C}_{38}\text{H}_{59}\text{FO}_6$ ); diflorasone ((6 $\alpha$ ,11 $\beta$ ,16 $\beta$ )-6,9-difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), or its diacetate form ( $\text{C}_{26}\text{H}_{32}\text{F}_2\text{O}_7$ ); diflucortolone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6,9-difluoro-11,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione),



or its 21-valerate form ( $C_{27}H_{36}F_2O_5$ ); difluprednate ((6 $\alpha$ ,11 $\beta$ )-21-(acetyloxy)-6,9-difluoro-11-hydroxy-17-(1-oxobutoxy)pregna-1,4-diene-3,20-dione); enoxolone ((3 $\beta$ ,20 $\beta$ )-3-hydroxy-11-oxoolean-12-en-29-oic acid), or its 18 $\alpha$ -hydrogen form; fluazacort ((11 $\beta$ ,16 $\beta$ )-21-(acetyloxy)-9-fluoro-11-hydroxy-2'-methyl-5'H-pregna-1,4-dieno[17,16-d]oxazole-3,20-dione); flucoronide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-9,11-dichloro-6-fluoro-21-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione); flumethasone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6,9-difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{24}H_{30}F_2O_6$ ), or its 21-pivalate form ( $C_{27}H_{36}F_2O_6$ ); flunisolide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene) bis(oxy)]pregna-1,4-diene-3,20-dione), or its 21-acetate form ( $C_{26}H_{33}FO_7$ ); fluocinolone acetate ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione); fluocinonide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-21-(acetyloxy)-6,9-difluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione); fluocortin butyl ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11-hydroxy-16-methyl-3,20-dioxopregna-1,4-dien-21-oic acid butyl ester); fluocortolone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{24}H_{31}FO_5$ ), its 21-hexanoate form ( $C_{28}H_{39}FO_5$ ), or its 21-pivalate form ( $C_{22}H_{37}FO_5$ ); fluorometholone ((6 $\alpha$ ,11 $\beta$ )-9-fluoro-11,17-dihydroxy-6-methylpregna-1,4-diene-3,20-dione), or its 17-acetate form ( $C_{24}H_{31}FO_5$ ); fluperolone acetate ((11 $\beta$ ,17 $\alpha$ ,17(S))-17-[2-(acetyloxy)-1-oxopropyl]-9-fluoro-11,17-dihydroxyandrosta-1,4-dien-3-one); fluprednidene acetate ((11 $\beta$ )-21-(acetyloxy)-9-fluoro-11,17-dihydroxy-16-methylenepregna-1,4-diene-3,20-dione); fluprednisolone ((6 $\alpha$ ,11 $\beta$ )-6-fluoro-11,17,21-trihydroxypregna-1,4-diene-3,20-dione), or its 21-acetate form ( $C_{23}H_{29}FO_6$ ); flurandrenolide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-4-ene-3,20-dione); fluticasone propionate ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ ,17 $\alpha$ )-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid S-(fluoromethyl) ester); formocortol ((11 $\beta$ ,16 $\alpha$ )-21-(acetyloxy)-3-(2-chloroethoxy)-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-20-oxopregna-3,5-diene-6-carboxaldehyde); halcinonide ((11 $\beta$ ,16 $\alpha$ )-21-chloro-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-4-ene-3,20-dione); halobetasol propionate (6 $\alpha$ ,11 $\beta$ ,16 $\beta$ )-21-chloro-6,9-difluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)pregna-1,4-diene-3,20-dione); halometasone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-2-chloro-6,9-difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), or its monohydrate form ( $C_{22}H_{27}ClF_2O_5 \cdot H_2O$ ); halopredone acetate ((6 $\beta$ ,11 $\beta$ )-17,21-bis(acetyloxy)-2-bromo-6,9-difluoro-11-hydroxypregna-1,4-diene-3,20-dione); hydrocortamate (N,N-diethylglycine (11 $\beta$ )-11,17-dihydroxy-3,20-dioxopregna-4-en-21-yl ester), or its hydrochloride form ( $C_{27}H_{41}NO_6 \cdot HCl$ ); hydrocortisone ((11 $\beta$ )-11,17,21-trihydroxypregna-4-ene-3,20-dione), its 21-acetate form ( $C_{23}H_{32}O_6$ ), its 17-butyrate form ( $C_{25}H_{36}O_6$ ), its 21-phosphate disodium salt form ( $C_{21}H_{29}Na_2O_8P$ ), its 21-sodium succinate form ( $C_{25}H_{33}NaO_8$ ), its 17-valerate form ( $C_{26}H_{38}O_6$ ), or its cypionate form; loteprednol etabonate ((11 $\beta$ ,17 $\alpha$ )-17-[(ethoxycarbonyl)oxy]-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylic acid chloromethyl ester); mazipredone ((11 $\beta$ )-11,17-dihydroxy-21-(4-methyl-1-piperazinyl)pregna-1,4-diene-3,20-dione), or its hydrochloride form ( $C_{26}H_{38}N_2O_4 \cdot HCl$ ); medrysone ((6 $\alpha$ ,11 $\beta$ )-11-hydroxy-6-methylpregna-4-ene-3,20-dione); meprednisone ((16 $\beta$ )-17,21-dihydroxy-16-methylpregna-1,4-diene-3,11,20-trione), or its 21-acetate form ( $C_{24}H_{30}O_6$ ); methylprednisolone ((6 $\alpha$ ,11 $\beta$ )-11,17,21-trihydroxy-6-methylpregna-1,4-diene-3,20-dione; Sebek and Spero, US Patent No. 2,897,218, and Gould, US Patent No. 3,053,832), its 21-acetate form ( $C_{24}H_{32}O_6$ ), its 21-phosphate disodium salt form ( $C_{22}H_{29}Na_2O_8P$ ), its 21-succinate sodium salt form ( $C_{26}H_{33}NaO_8$ ), or its aceponate form ( $C_{27}H_{36}O_7$ ); mometasone furoate ((11 $\beta$ ,16 $\alpha$ )-9,21-dichloro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methylpregna-1,4-diene-3,20-dione); paramethasone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{24}H_{31}FO_6$ ), its disodium phosphate form, or a mixture of its 21-acetate and disodium phosphate form; prednicarbate ((11 $\beta$ )-17[(ethoxycarbonyl)oxy]-11-hydroxy-21-(1-oxopropoxy)pregna-1,4-diene-3,20-dione); prednisolone ((11 $\beta$ )-11,17,21-trihydroxypregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{23}H_{30}O_6$ ), its 21-*tert*-butylacetate form ( $C_{27}H_{38}O_6$ ; Sarrett), its 21-hydrogen succinate form ( $C_{25}H_{32}O_8$ ), its 21-succinate sodium salt form ( $C_{25}H_{31}NaO_8$ ), its 21-stearoylglycolate form ( $C_{41}H_{64}O_8$ ), its 21-*m*-sulphobenzoate sodium salt form ( $C_{28}H_{31}NaO_9S$ ; (11 $\beta$ )-11,17-dihydroxy-21-[(3-sulphobenzoyl)oxy]pregna-1,4-diene-3,20-dione monosodium salt), or its 21-trimethylacetate form ( $C_{26}H_{36}O_6$ ); prednisolone 21-diethylaminoacetate (N,N-diethylglycine (11 $\beta$ )-11,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl ester; British Patent No. 862,370), or its hydrochloride form ( $C_{27}H_{39}NO_6 \cdot HCl$ ); prednisolone sodium phosphate (11,17-dihydroxy-21-(phosphonoxy)pregna-1,4-diene-3,20-dione disodium salt); prednisone (17,21-dihydroxypregna-1,4-diene-3,11,20-trione), or its 21-acetate form ( $C_{23}H_{28}O_6$ ); prednival ((11 $\beta$ )-11,21-dihydroxy-17-[(1-oxopentyl)oxy]pregna-1,4-

diene-3,20-dione;), or its 21-acetate form ( $C_{28}H_{38}O_7$ ); prednylidene ((11 $\beta$ )-11,17,21-trihydroxy-16-methylenepregna-1,4-diene-3,20-dione), or its 21-diethylaminoacetate hydrochloride form ( $C_{28}H_{39}NO_6 \cdot HCl$ ); rimexolone ((11 $\beta$ ,16 $\alpha$ ,17 $\beta$ )-11-hydroxy-16,17-dimethyl-17-(1-oxopropyl)androsta-1,4-dien-3-one); rofleponide ((22R)-6 $\alpha$ ,9 $\alpha$ -Difluoro-11 $\beta$ ,21-dihydroxy-16 $\alpha$ ,17 $\alpha$ -propylmethylenedioxypregn-4-ene-3,20-dione); tipredane ((11 $\beta$ , 17 $\alpha$ )-17-(ethylthio)-9 $\alpha$ -fluoro-11 $\beta$ -hydroxy-17-(methylthio) androsta-1,4-dien-3-one); tixocortol ((11 $\beta$ )-11,17-dihydroxy-21-mercaptopregn-4-ene-3,20-dione), or its 21-pivalate form ( $C_{26}H_{38}O_5S$ ; (11 $\beta$ )-21-[(2,2-dimethyl-1-oxopropyl)thio]-11,17-dihydroxypregn-4-ene-3,20-dione); triamcinolone ((11 $\beta$ ,16 $\alpha$ )-9-fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione), or its 16,21-diacetate form ( $C_{25}H_{31}FO_8$ ; (11 $\beta$ ,16 $\alpha$ )-16,21-bis(acetyloxy)-9-fluoro-11,17-dihydroxypregna-1,4-diene-3,20-dione); Triamcinolone acetone ((11 $\beta$ ,16 $\alpha$ )-9-fluoro-11,21-dihydroxy-16,17-[1-methylethylidenebis(oxy)]pregna-1,4-diene-3,20-dione), its 21-acetate crystal form, its 21-disodium phosphate form ( $C_{24}H_{30}FNa_2O_9P$ ), or its 21-hemisuccinate form ( $C_{28}H_{35}FO_9$ ); triamcinolone benetonide ((11 $\beta$ ,16 $\alpha$ )-21-[3-(benzoylamino)-2-methyl-1-oxopropoxy]-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione); or triamcinolone hexacetone; ((11 $\beta$ ,16 $\alpha$ )-21-(3,3-dimethyl-1-oxobutoxy)-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione), analogues thereof, or pharmaceutically or veterinarily acceptable salts thereof.

35. The composition of claim 1, wherein the second agent comprises a glucocorticoid steroid selected from budesonide, testosterone, progesterone, estrogen, flunisolide, triamcinolone, beclomethasone, betamethasone, dexamethasone, fluticasone, methylprednisolone, prednisone, hydrocortisone, or mometasone.
36. The composition of claim 1, wherein the first active agent comprises a single stranded anti-sense DNA oligo.
37. The composition of claim 1, wherein the first active agent comprise(s) a double stranded DNA oligo.
38. The composition of claim 1, wherein the first active agent comprises a single stranded anti-sense RNA oligo(s).
39. The composition of claim 1, wherein the first active agent comprises a double stranded RNA oligo(s).
40. The composition of claim 1, which is a systemic or topical formulation.
41. The formulation of claim 40, selected from oral, intrabuccal, intrapulmonary, rectal, intrauterine, intratumor, intracranial, nasal, intramuscular, subcutaneous, intravascular, intrathecal, inhalable, transdermal, intradermal, intracavitary, implantable, iontophoretic, ocular, vaginal, intraarticular, otical, intravenous, intramuscular, intraglandular, intraorgan, intralymphatic, implantable, slow release or enteric coating formulations.
42. The formulation of claim 41, which is an oral formulation, wherein the carrier is selected from solid or liquid carriers.
43. The formulation of claim 42, in the form of a powder, dragees, tablets, capsules, sprays, aerosols, solutions, suspensions and emulsions, or optionally oil-in-water or water-in-oil emulsions.
44. The formulation of claim 41, which is a topical formulation, in the form of cream, gel, ointment, spray, aerosol, patch, solution, suspension or emulsion.
45. The formulation of claim 41, which is an injectable formulation, in the form of an aqueous or alcoholic solution or suspension, an oily solution or suspension, or an oil-in-water or water-in-oil emulsion.
46. The formulation of claim 41, in the form of a rectal or vaginal formulation, optionally a suppository.
47. The formulation of claim 41, in the form of a transdermal formulation, wherein the carrier comprises an aqueous or alcoholic solution, an oily solution or suspension, or an oil-in-water or water-in-oil emulsion.
48. The formulation of claim 47, in the form of an iontophoretic transdermal formulation, wherein the carrier comprises an aqueous or alcoholic solution, an oily solution or suspension, or an oil-in-water or water-in-oil emulsion, and wherein the formulation further comprises a transdermal transport promoting agent.
49. The formulation of claim 41, in the form of an implant, a capsule, a cartridge or a blister.
50. The formulation of claim 49, in the form of an aqueous or alcoholic solution or suspension, an oily solution or suspension, or an oil-in-water or water-in-oil emulsion.
51. The formulation of claim 40, wherein the carrier comprises a hydrophobic carrier.

52. The formulation of claim 51, wherein the carrier comprises lipid vesicles, optionally liposomes; or particles, optionally microcrystals.

53. The formulation of claim 52, wherein the carrier comprises liposomes, and the liposomes comprise the active agent(s).

54. The formulation of claim 41, which is a respirable or inhalable formulation, optionally aerosolizable or sprayable of particle size about 0.05 to about 10 micron.

55. The formulation of claim 54, having a particle size about 0.1 to about 5 micron.

56. The formulation of claim 41, which is a nasal or intrapulmonary formulation, optionally aerosolizable or sprayable of particle size about 8 to about 200 micron.

57. The formulation of claim 56, of particle size about 10 to about 50 micron.

58. The formulation of claim 41, in single or multiple unit form.

59. The formulation of claim 41, in bulk.

60. A therapeutic or prophylactic kit, comprising a delivery device; in separate containers, the active agent(s) of claim 1; and instructions for adding a carrier and preparing a formulation and for use of the kit.

61. The kit of claim 60, wherein the device delivers single metered doses of the formulation.

62. The kit of claim 60, wherein the formulation is a respirable formulation, and the delivery device comprises a nebulizer or a dry powder inhaler.

63. The kit of claim 62, wherein the device comprises a nebulizer or an insufflator and the formulation is provided in a piercable or openable capsule or cartridge.

64. The kit of claim 60, wherein the delivery device comprises a pressurized inhaler and the agent(s) is (are) provided as a suspension, solution or dry formulation of the active agent(s).

65. The kit of claim 60, further comprising, in a separate container, an agent selected from other therapeutic agents, surfactants, anti-oxidants, flavoring agents, fillers, volatile oils, dispersants, antioxidants, propellants, preservatives, buffering agents, RNA inactivating agents, cell-internalized or up-taken agents or coloring agents.

66. The kit of claim 60, comprising, in separate containers, one or more oligos, one or more AIS of formula (Ia), or (Ib) one or more surfactants, a carrier or diluent, optionally other therapeutic agents, and instructions for scheduling the administration of first and second agents.

67. The kit of claim 66, further comprising one or more ubiquinone(s), and instructions for scheduling the administration of first and second agents.

68. The kit of claim 60, wherein the device is a transdermal delivery device, and the kit further comprises a transdermal delivery agent, a transdermal carrier or diluent, and instructions for preparing and delivering a transdermal delivery formulation.

69. The kit of claim 60, wherein the device is an iontophoretic delivery device, and the kit further comprises an iontophoretic agent(s) and instructions for preparing and delivering an iontophoretic formulation.

70. The kit of claim 60, comprising, in separate containers, one or more oligo(s), one or more ubiquinone(s), one or more surfactants, a carrier or diluent, optionally other therapeutic agents, and instructions for scheduling the administration of first and second agents.

71. A method of preventing or treating a respiratory, lung or malignant disease or condition, comprising simultaneously, sequentially or separately administering to a subject in need of treatment, preventative, prophylactic or therapeutic amounts of the first and second active agents of claim 1.

72. The method of claim 71, wherein the oligo(s) and the AIS are administered in amounts effective for alleviating bronchoconstriction and/or lung inflammation or allergy(ies) and/or surfactant depletion or hyposecretion.

73. The method of claim 71, wherein the oligo(s) and the ubiquinone(s) are administered in amounts effective for alleviating bronchoconstriction, lung inflammation or allergies, or ubiquinone or lung surfactant depletion.

74. The method of claim 71, wherein one or more of the agent(s) is (are) administered as a nasal, inhalable, respirable or intrapulmonary composition(s) into the subject's respiratory system.

75. The method of claim 74, wherein one or more of the agents are administered intrapulmonarily or by inhalation.

76. The method of claim 74, wherein the respirable or inhalable composition(s) comprise(s) particles

about 0.05 to about 10 micron in size.

77. The method of claim 74, wherein the nasal or intrapulmonary composition comprises particles about 8 to about 100 micron in diameter.

78. The method of claim 74, wherein the composition(s) is (are) administered as a respirable aerosol.

79. The method of claim 71, wherein the ubiquinone(s) is (are) administered orally, and the oligo(s) and the AIS are administered through the respiratory tract.

80. The method of claim 71, wherein the disease or condition is associated with pulmonary obstruction, bronchoconstriction, lung inflammation or allergy(ies), adenosine hypersensitivity, adenosine or adenosine receptor(s), hyperproduction, or surfactant or ubiquinone hypoproduction.

81. The method of claim 71, wherein the disease or condition comprises pulmonary vasoconstriction, respiratory inflammation or allergies, asthma, impeded respiration, respiratory distress syndrome (RDS), lung pain, cystic fibrosis (CF), allergic rhinitis (AR), apnea, pulmonary hypertension, emphysema, chronic obstructive pulmonary disease (COPD), pulmonary transplantation rejection, pulmonary fibrosis, pulmonary infections, bronchitis, or cancer.

82. The method of claim 71, wherein the disease or condition is associated with respiratory allergies, and the first active agent(s) is anti-sense to the initiation codon, the coding region, the 5'-end or the 3'-end genomic flanking regions, the 5' or 3' intron-exon junctions, or regions within 2 to 10 nucleotides of the junctions of at least one gene(s) encoding, or regulating expression of, an immunoglobulin(s), antibody(ies), or immunoglobulin or antibody receptors, or are anti-sense to the immunoglobulin(s), antibody(ies), or immunoglobulin or antibody receptor mRNA; MTAs of the oligo(s) or combinations thereof.

83. The method of claim 71, wherein the disease or condition is associated with a malignancy or cancer, and the oligo is anti-sense to the initiation codon, the coding region, the 5'-end or the 3'-end genomic flanking regions, the 5' or 3' intron-exon junctions, or regions within 2 to 10 nucleotides of the junctions of an oncogene(s) or at least one gene that regulates expression of, or encodes, a malignancy associated protein, or is(are) anti-sense to the oncogene or malignancy associated mRNA; MTAs or combinations thereof.

84. The method of claim 71, wherein the composition is administered transdermally or systemically.

85. The method of claim 71, wherein the composition is administered orally, intracavitarily, intranasally, intraurethral, intracavernous, intraanally, intravaginally, intrauterally, intraarticularly, transdermally, intrabuccally, intravenously, subcutaneously, intramuscularly, intravascularly, intratumorously, intraglandularly, intraocularly, intracranial, into an organ, intravascularly, intrathecally, intralymphatically, intraotically, by implantation, by inhalation, intradermally, intrapulmonarily, intraotically, by slow release, by sustained release and by a pump.

86. The method of claim 71, wherein the mammal(s) is a human or non-human mammal.

87. The method of claim 71, wherein the oligo(s) is (are) administered in amount of about 0.005 to about 150 mg/kg body weight.

88. The method of claim 71, wherein the oligo(s) contain(s) up to about 15%A.

89. The method of claim 71, wherein the oligo(s) is (are) substantially free of A.

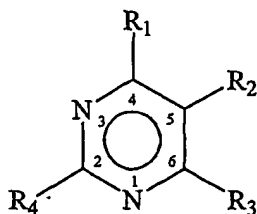
90. The method of claim 71, wherein the target comprises transcription factors, stimulating or activating factors, interleukins, interleukin receptors, chemokines, chemokine receptors, endogenously produced specific or non-specific enzymes, immunoglobulins, antibody receptors, central nervous system (CNS) or peripheral nervous or non-nervous system receptors, CNS and peripheral nervous and non-nervous system peptide transmitters, adhesion molecules, defensins, growth factors, microbial targets, vasoactive peptides, peptide receptors or binding proteins, or malignancy associated proteins.

91. The method of claim 71, wherein one or more As in the oligo(s) is(are) substituted by a universal base that comprise(s) a heteroaromatic base(s) that bind(s) to thymidine or uridine but has(have) less than about 0.3 of the adenosinebase agonist or antagonist activity at an adenosine A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub> or A<sub>3</sub> receptor.

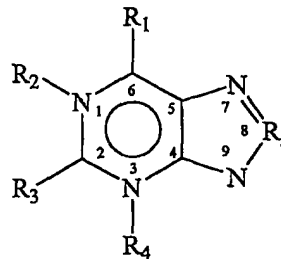
92. The method of claim 91, wherein the heteroaromatic base(s) comprise(s) pyrimidines or purines, which may be substituted by O, halo, NH<sub>2</sub>, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>, COOH, branched or fused primary or secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, all of which may be further substituted by O, halo, NH<sub>2</sub>, primary, secondary or tertiary amine, SH, SO, SO<sub>2</sub>, SO<sub>3</sub>,

cycloalkyl, heterocycloalkyl or heteroaryl.

93. The method of claim 91, wherein the purines are substituted at positions 1, 2, 3, 6, and/or 8, the pyrimidines are substituted at positions 2, 3, 4, 5 and/or 6 and have the chemical formula



pyrimidines



purines

or

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are independently H, alkyl, alkenyl or alkynyl and  $R^3$  is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkenyl, O-cycloalkynyl,  $NH_2$ -alkylamino-ketoxyalkyloxy-aryl, or mono or dialkylaminoalkyl-N-alkylamino- $SO_2$ aryl, and  $R^4$  and  $R^5$  are independently  $R^1$  and together are  $R^3$ , and the pyrimidines and purines optionally comprise theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline or xanthine.

94. The method of claim 93, wherein the universal base(s) comprise(s) 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one, or 2-amino-6-methoxyaminopurine.

95. The method of claim 71, wherein the second active agent comprises an AIS of formula (Ia) selected from dehydroepiandrosterone, 16- $\alpha$ -bromodehydroepiandrosterone, 16- $\alpha$ -fluorodehydroepiandrosterone, etiocholanolone, dehydroepiandrosterone sulfate or other pharmaceutically or veterinarily acceptable salts thereof.

96. The method of claim 71, wherein the second active agent comprises an AIS formula (Ib), wherein  $R^{15}$  and  $R^{16}$  together are  $=O$ ;  $R^5$  is  $-OH$ ;  $R^5$  is  $-OSO_2R^{20}$ ;  $R^{15}$  and  $R^{20}$  together is H; or pharmaceutically or veterinarily acceptable salts thereof.

97. The method of claim 71, wherein the active agents are present in an amount of about 0.01 to about 99.99 w/w of the composition.

98. The method of claim 71, wherein the second active agent comprises an AIS selected from 21-acetoxypregnenolone ((3 $\beta$ )-21-(acetyloxy)-3-hydroxypregn-5-en-20-one); alclometasone ((7 $\alpha$ , 11 $\beta$ , 16 $\alpha$ )-7-Chloro-11, 17, 21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), or its 17,21-dipropionate form ( $C_{28}H_{37}ClO_7$ ); algestone ((16 $\alpha$ )-16,17-dihydroxypregn-4-ene-3,20-dione), its cyclic acetal with acetone form ( $C_{24}H_{34}O_4$ ), or its 16 $\alpha$ -methyl ether form ( $C_{22}H_{32}O_4$ ); amcinonide ((11 $\beta$ , 16 $\alpha$ )-21-(acetyloxy)-16,17-[cyclopentylidenebis(oxy)]-9-fluoro-11-hydroxypregna-1,4-di-ene-3,20-dione); beclomethasone ((11 $\beta$ ,16 $\beta$ )-9-chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), its dipropionate form ( $C_{28}H_{37}ClO_7$ ), or its monopropionate form; betamethasone ((11 $\beta$ , 16 $\beta$ )-9-fluoro-11, 17, 21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{24}H_{31}FO_6$ ), its 21-adamantoate form ( $C_{33}H_{43}FO_6$ ), its 17-benzoate form ( $C_{29}H_{33}FO_6$ ), its 17, 21-dipropionate form ( $C_{28}H_{37}FO_7$ ), its 17-valerate form ( $C_{27}H_{37}FO_6$ ), or its 21-phosphate disodium salt form ( $C_{22}H_{28}FN_2O_8P$ ); budesonide ((11 $\beta$ , 16 $\alpha$ )-16,17-[butylidenebis(oxy)]-11, 21-dihydropregna-1,4-diene-3,20-dione); chloroprednisone ((6 $\alpha$ )-chloro-17,21-dihydroxypregna-1,4-diene-3,11,20-trione), or its 21-acetate from ( $C_{23}H_{27}ClO_6$ ); ciclesonide; clobetasol ((11 $\beta$ ,16 $\beta$ )-21-chloro-9-fluoro-11,17-dihydroxy-16-methylpregna-1,4-diene-3,20-dione), or its 17-propionate form ( $C_{25}H_{32}ClFO_5$ ); clobetasone ((16 $\beta$ )-21-chloro-9-fluoro-17-hydroxy-16-methylpregna-1,4-diene-3,11,20-trione), or its 17-butyrate form ( $C_{26}H_{32}ClFO_5$ ); clocortolone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-9-chloro-6-fluoro-11,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{24}H_{30}ClFO_5$ ), or its 21-pivalate form ( $C_{27}H_{36}ClFO_5$ ); cloprednol ((11 $\beta$ )-6-chloro-11,17,21-trihydroxypregna-1,4,6-triene-3,20-dione); coroxon

(phosphoric acid 3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl diethyl ester); cortisone (17,21-dihydroxypregn-4-ene-3,11,20-trione), its 21-acetate form ( $C_{23}H_{30}O_6$ ), or its 21-cyclopentanepropionate form ( $C_{29}H_{40}O_6$ ); cortivazol ((11 $\beta$ ,16 $\alpha$ )-21-(acetyloxy)-11,17-dihydroxy-6,16-dimethyl-2'-phenyl-2'H-pregna-2,4,6-trieno[3,2-c]pyrazol-20-one); deflazacort ((11 $\beta$ ,16 $\beta$ )-21-(acetyloxy)-11-hydroxy-2'-methyl-5'H-pregna-1,4-dieno[17,16-d]oxazole-3,20-dione); desonide ((11 $\beta$ ,16 $\alpha$ )-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione); desoximetasone ((11 $\beta$ ,16 $\alpha$ )-9-fluoro-11, 21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione); dexamethasone ((11 $\beta$ ,16 $\alpha$ )-9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{24}H_{31}FO_6$ ), its 21-(3,3-dimethylbutyrate) form ( $C_{28}H_{39}FO_6$ ; Chimerda et al., US Patent No. 2,939,873), its 21-diethylaminoacetate form ( $C_{28}H_{41}FNO_6$ ), its 21-isonicotinate form ( $C_{28}H_{41}FNO_6$ ), its 17,21-dipropionate form ( $C_{28}H_{37}FNO_6$ ), or its 21-palmitate form ( $C_{38}H_{59}FO_6$ ); diflorasone ((6 $\alpha$ ,11 $\beta$ ,16 $\beta$ )-6,9-difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), or its diacetate form ( $C_{26}H_{32}F_2O_7$ ); diflucortolone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6,9-difluoro-11,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione), or its 21-valerate form ( $C_{27}H_{36}F_2O_5$ ); difluprednate ((6 $\alpha$ ,11 $\beta$ )-21-(acetyloxy)-6,9-difluoro-11-hydroxy-17-(1-oxobutoxy)pregna-1,4-diene-3,20-dione); enoxolone ((3 $\beta$ ,20 $\beta$ )-3-hydroxy-11-oxoolean-12-en-29-oic acid), or its 18 $\alpha$ -hydrogen form; fluazacort ((11 $\beta$ ,16 $\beta$ )-21-(acetyloxy)-9-fluoro-11-hydroxy-2'-methyl-5'H-pregna-1,4-dieno[17,16-d]oxazole-3,20-dione); flucoronide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-9,11-dichloro-6-fluoro-21-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione); flumethasone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6,9-difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{24}H_{30}F_2O_6$ ), or its 21-pivalate form ( $C_{27}H_{36}F_2O_6$ ); flunisolide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene) bis(oxy)]pregna-1,4-diene-3,20-dione), or its 21-acetate form ( $C_{26}H_{33}FO_7$ ); fluocinolone acetate ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione); fluocinonide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-21-(acetyloxy)-6,9-difluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione); fluocortin butyl ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11-hydroxy-16-methyl-3,20-dioxopregna-1,4-dien-21-oic acid butyl ester); fluocortolone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{24}H_{31}FO_5$ ), its 21-hexanoate form ( $C_{28}H_{39}FO_5$ ), or its 21-pivalate form ( $C_{22}H_{37}FO_5$ ); fluorometholone ((6 $\alpha$ ,11 $\beta$ )-9-fluoro-11,17-dihydroxy-6-methylpregna-1,4-diene-3,20-dione), or its 17-acetate form ( $C_{24}H_{31}FO_5$ ); fluperolone acetate ([11 $\beta$ ,17 $\alpha$ ,17(S)]-17-[2-(acetyloxy)-1-oxopropyl]-9-fluoro-11,17-dihydroxyandrost-1,4-dien-3-one); fluprednidene acetate ((11 $\beta$ )-21-(acetyloxy)-9-fluoro-11,17-dihydroxy-16-methylenepregna-1,4-diene-3,20-dione); fluprednisolone ((6 $\alpha$ ,11 $\beta$ )-6-fluoro-11,17,21-trihydroxypregna-1,4-diene-3,20-dione), or its 21-acetate form ( $C_{23}H_{29}FO_6$ ); flurandrenolide ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregn-4-ene-3,20-dione); fluticasone propionate ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ ,17 $\alpha$ )-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androst-1,4-diene-17-carbothioic acid S-(fluoromethyl) ester); formocortol ((11 $\beta$ ,16 $\alpha$ )-21-(acetyloxy)-3-(2-chloroethoxy)-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-20-oxopregna-3,5-diene-6-carboxaldehyde); halcinonide ((11 $\beta$ ,16 $\alpha$ )-21-chloro-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregn-4-ene-3,20-dione); halobetasol propionate ((6 $\alpha$ ,11 $\beta$ ,16 $\beta$ )-21-chloro-6,9-difluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)pregna-1,4-diene-3,20-dione); halometasone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-2-chloro-6,9-difluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), or its monohydrate form ( $C_{22}H_{27}ClF_2O_5 \cdot H_2O$ ); halopredone acetate ((6 $\beta$ ,11 $\beta$ )-17,21-bis(acetyloxy)-2-bromo-6,9-difluoro-11-hydroxypregna-1,4-diene-3,20-dione); hydrocortamate (N,N-diethylglycine (11 $\beta$ )-11,17-dihydroxy-3,20-dioxopregna-4-en-21-yl ester), or its hydrochloride form ( $C_{27}H_{41}NO_6 \cdot HCl$ ); hydrocortisone ((11 $\beta$ )-11,17,21-trihydroxypregna-4-ene-3,20-dione), its 21-acetate form ( $C_{23}H_{32}O_6$ ), its 17-butyrate form ( $C_{25}H_{36}O_6$ ), its 21-phosphate disodium salt form ( $C_{21}H_{29}Na_2O_8P$ ), its 21-sodium succinate form ( $C_{25}H_{33}NaO_8$ ), its 17-valerate form ( $C_{26}H_{38}O_6$ ), or its cypionate form; loteprednol etabonate ((11 $\beta$ ,17 $\alpha$ )-17-[(ethoxycarbonyl)oxy]-11-hydroxy-3-oxoandrost-1,4-diene-17-carboxylic acid chloromethyl ester); mazipredone ((11 $\beta$ )-11,17-dihydroxy-21-(4-methyl-1-piperazinyl)pregna-1,4-diene-3,20-dione), or its hydrochloride form ( $C_{26}H_{38}N_2O_4 \cdot HCl$ ); medrysone ((6 $\alpha$ ,11 $\beta$ )-11-hydroxy-6-methylpregn-4-ene-3,20-dione); meprednisone ((16 $\beta$ )-17,21-dihydroxy-16-methylpregna-1,4-diene-3,11,20-trione), or its 21-acetate form ( $C_{24}H_{30}O_6$ ); methylprednisolone ((6 $\alpha$ ,11 $\beta$ )-11,17,21-trihydroxy-6-methylpregna-1,4-diene-3,20-dione; Sebek and Spero, US Patent No. 2,897,218, and Gould, US Patent No. 3,053,832), its 21-acetate form ( $C_{24}H_{32}O_6$ ), its 21-phosphate disodium salt form ( $C_{22}H_{29}Na_2O_8P$ ), its 21-succinate sodium salt form ( $C_{26}H_{33}NaO_8$ ), or its aceponate form ( $C_{27}H_{36}O_7$ ); mometasone furoate ((11 $\beta$ ,16 $\alpha$ )-9,21-dichloro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methylpregna-1,4-diene-3,20-dione); paramethasone ((6 $\alpha$ ,11 $\beta$ ,16 $\alpha$ )-6-

fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{24}H_{31}FO_6$ ), its disodium phosphate form, or a mixture of its 21-acetate and disodium phosphate form; prednicarbate ((11 $\beta$ )-17[(ethoxycarbonyl)oxy]-11-hydroxy-21-(1-oxopropoxy)pregna-1,4-diene-3,20-dione); prednisolone ((11 $\beta$ )-11,17,21-trihydroxypregna-1,4-diene-3,20-dione), its 21-acetate form ( $C_{23}H_{30}O_6$ ), its 21-*tert*-butylacetate form ( $C_{27}H_{38}O_6$ ; Sarrett), its 21-hydrogen succinate form ( $C_{25}H_{32}O_8$ ), its 21-succinate sodium salt form ( $C_{25}H_{31}NaO_8$ ), its 21-stearoylglycolate form ( $C_{41}H_{64}O_8$ ), its 21-*m*-sulfobenzoate sodium salt form ( $C_{28}H_{31}NaO_9S$ ; (11 $\beta$ )-11,17-dihydroxy-21-[(3-sulfobenzoyl)oxy]pregna-1,4-diene-3,20-dione monosodium salt), or its 21-trimethylacetate form ( $C_{26}H_{36}O_6$ ); prednisolone 21-diethylaminoacetate (N,N-diethylglycine (11 $\beta$ )-11,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl ester; British Patent No. 862,370), or its hydrochloride form ( $C_{27}H_{39}NO_6 \cdot HCl$ ); prednisolone sodium phosphate (11,17-dihydroxy-21-(phosphonooxy)pregna-1,4-diene-3,20-dione disodium salt); prednisone (17,21-dihydroxypregna-1,4-diene-3,11,20-trione), or its 21-acetate form ( $C_{23}H_{28}O_6$ ); prednival ((11 $\beta$ )-11,21-dihydroxy-17-[(1-oxopentyl)oxy]pregna-1,4-diene-3,20-dione), or its 21-acetate form ( $C_{28}H_{38}O_7$ ); prednylidene ((11 $\beta$ )-11,17,21-trihydroxy-16-methylenepregna-1,4-diene-3,20-dione), or its 21-diethylaminoacetate hydrochloride form ( $C_{28}H_{39}NO_6 \cdot HCl$ ); rimexolone ((11 $\beta$ ,16 $\alpha$ ,17 $\beta$ )-11-hydroxy-16,17-dimethyl-17-(1-oxopropyl)androst-1,4-dien-3-one); rofleponide ((2R)-6 $\alpha$ ,9 $\alpha$ -Difluoro-11 $\beta$ ,21-dihydroxy-16 $\alpha$ ,17 $\alpha$ -propylmethylenedioxypregn-4-ene-3,20-dione); tipredane ((11 $\beta$ , 17 $\alpha$ )-17-(ethylthio)-9 $\alpha$ -fluoro-11 $\beta$ -hydroxy-17-(methylthio) androst-1,4-dien-3-one); tixocortol ((11 $\beta$ )-11,17-dihydroxy-21-mercaptopregn-4-ene-3,20-dione), or its 21-pivalate form ( $C_{26}H_{38}O_5S$ ; (11 $\beta$ )-21-[(2,2-dimethyl-1-oxopropyl)thio]-11,17-dihydroxypregn-4-ene-3,20-dione); triamcinolone ((11 $\beta$ ,16 $\alpha$ )-9-fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione), or its 16,21-diacetate form ( $C_{25}H_{31}FO_8$ ; (11 $\beta$ ,16 $\alpha$ )-16,21-bis(acetyloxy)-9-fluoro-11,17-dihydroxypregna-1,4-diene-3,20-dione); Triamcinolone acetone ((11 $\beta$ ,16 $\alpha$ )-9-fluoro-11,21-dihydroxy-16,17-[1-methylethylidenebis(oxy)]pregna-1,4-diene-3,20-dione), its 21-acetate crystal form, its 21-disodium phosphate form ( $C_{24}H_{30}FNa_2O_9P$ ), or its 21-hemisuccinate form ( $C_{28}H_{33}FO_9$ ); triamcinolone benetonide ((11 $\beta$ ,16 $\alpha$ )-21-[3-(benzoylamino)-2-methyl-1-oxopropoxy]-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione); or triamcinolone hexacetone;((11 $\beta$ ,16 $\alpha$ )-21-(3,3-dimethyl-1-oxobutoxy)-9-fluoro-11-hydroxy-16,17-[(1-methylethylidene) bis(oxy)]pregna-1,4-diene-3,20-dione), or pharmaceutically or veterinarily acceptable salts thereof.

99. The method of claim 71, wherein the second active agent comprises an AIS selected from budesonide, testosterone, progesterone, estrogen, flunisolide, triamcinolone, beclomethasone, betamethasone, dexamethasone, fluticasone, methylprednisolone, prednisone, hydrocortisone, or mometasone.

100. A method of enhancing the prophylactic or therapeutic respiratory effect of an anti-inflammatory steroid in a subject, comprising administering to the subject, in addition to the AIS, the oligonucleotide(s) (oligo(s)) of claim 1, the AIS and the oligo(s) being administered in amounts effective for reducing or depleting levels of, or reducing sensitivity to, adenosine, reducing levels of adenosine receptors, producing bronchodilation, increasing levels of ubiquinone or lung surfactant in a subject's tissue (s), or treating bronchoconstriction, lung inflammation or lung allergies or a respiratory or lung disease or condition.

101. The method of claim 100, further administering to the subject a ubiquinone of the chemical formula.

102. The method of claim 100, wherein the steroid comprises budesonide, testosterone, progesterone, estrogen, flunisolide, triamcinolone, beclomethasone, betamethasone, dexamethasone, fluticasone, methylprednisolone, prednisone, hydrocortisone, or mometasone

103. The method of claim 100, wherein the oligo(s) is anti-sense to the initiation codon, the coding region, the 5'-end or the 3'-end genomic flanking regions, the 5' or 3' intron-exon junctions, and regions within 2 to 10 nucleotides of the junctions of at least one oncogene(s) and a gene(s) encoding or regulating expression of a target polypeptide(s) associated with lung airway dysfunction, or anti-sense to the corresponding mRNA and the polypeptide mRNA; combinations, MTAs or mixtures of the oligos; the polypeptides comprising peptide factors and transmitters, antibodies, cytokines or chemokines, enzymes, binding proteins, adhesion molecules, their receptors, or malignancy associated proteins.

104. The method of claim 100, further comprising administering to the subject other therapeutic or bioactive agents selected from analgesics, pre-menstrual medications, menopausal agents, anti-aging agents, anti-anxiety agents, mood disorder agents, anti-depressants, anti-bipolar mood agents, anti-schizophrenic agents, anti-cancer agents, alkaloids, blood pressure controlling agents, muscle relaxants, steroids, soporific agents, anti-



ischemic agents, anti-arrhythmic agents, contraceptives, vitamins, minerals, tranquilizers, neurotransmitter regulating agents, wound healing agents, anti-angiogenic agents, cytokines, growth factors, B-adrenergic receptor agonists, anti-metastatic agents, antacids, anti-histaminic agents, anti-bacterial agents, anti-viral agents, anti-gas agents, appetite suppressants, sun screens, emollients, skin temperature lowering products, radioactive phosphorescent or fluorescent contrast diagnostic or imaging agents, libido altering agents, bile acids, laxatives, anti-diarrheic agents, skin renewal agents, hair growth agents, analgesics, pre-menstrual medications, anti-menopausal agents, hormones, anti-aging agents, anti-anxiolytic agents, nociceptive agents, mood disorder agents, anti-depressants, anti-bipolar mood agents, anti-schizophrenic agents, anti-cancer agents, alkaloids, blood pressure controlling agents, other hormones, other anti-inflammatory agents, agents for treating arthritis, burns, wounds, chronic bronchitis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease such as Crohn's disease, ulcerative colitis, autoimmune disease, or lupus erythematosus, muscle relaxants, soporific agents, anti-ischemic agents, anti-arrhythmic agents, contraceptives, vitamins, minerals, tranquilizers, neurotransmitter regulating agents, wound and burn healing agents, anti-angiogenic agents, cytokines, growth factors, anti-metastatic agents, antacids, anti-histaminic agents, anti-bacterial agents, anti-viral agents, anti-gas agents, agents for reperfusion injury, counteracting appetite suppressants, sun screens, emollients, skin temperature lowering products, radioactive phosphorescent or fluorescent contrast diagnostic or imaging agents, libido altering agents, bile acids, laxatives, anti-diarrheic agents or skin renewal agents.

105. The method of claim 100, wherein the oligo(s) and/or the steroid(s) is(are) administered with surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant Protein E, disaturated phosphatidyl choline (other than dipalmitoyl), dipalmitoyl phosphatidyl choline, phosphatidyl choline, phosphatidyl glycerol, phosphatidyl inositol, phosphatidyl ethanolamine, phosphatidyl serine; phosphatidic acid, ubiquinones, lysophosphatidyl ethanolamine, lysophosphatidyl choline, palmitoyl-lysophosphatidyl choline, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycerol-3-phosphocholine, dihydroxy acetone, palmitate, cytidine diphosphate (CDP) diacyl glycerol, CDP choline, choline, choline phosphate; natural or artificial lamellar bodies as carrier surfactant vehicles, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitic acid, non-ionic block copolymers of ethylene or propylene oxides, polyoxypropylene, monomeric or polymeric, polyoxyethylene, monomeric and polymeric, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100 or synthetic surfactants ALEC, Exosurf, Survan or Atovaquone.

106. The method of claim 100, wherein the AIS comprises a steroid of chemical formula (Ia) or (Ib).

107. The method of claim 106, wherein the AIS is selected from budesonide, testosterone, progesterone, fluticasone, beclomethasone, prednisone, mometasone, estrogen, dexamethasone, hydrocortisone, triamcinolone, flunisolide, methylprednisolone prednisone, hydrocortisone, or analogues thereof.

108. The method of claim 100, wherein the first and second active agents are administered systemically or topically.

109. The method of claim 100, wherein the first and second active agents are administered as an oral, intrabuccal, intrapulmonary, rectal, intrauterine, intratumor, intracranial, nasal, intramuscular, subcutaneous, intravascular, intrathecal, inhalable, transdermal, intradermal, intracavitary, implantable, iontophoretic, ocular, vaginal, intraarticular, otical, intravenous, intramuscular, intraglandular, intraorgan, intralymphatic, implantable, slow release or enteric coating formulation.

110. The method of claim 101, wherein the ubiquinone is administered orally.

107. The method of claim 106, wherein the oligo(s) and the AIS is(are) administered intrapulmonarily, into the respiration, nasally, or by inhalation.

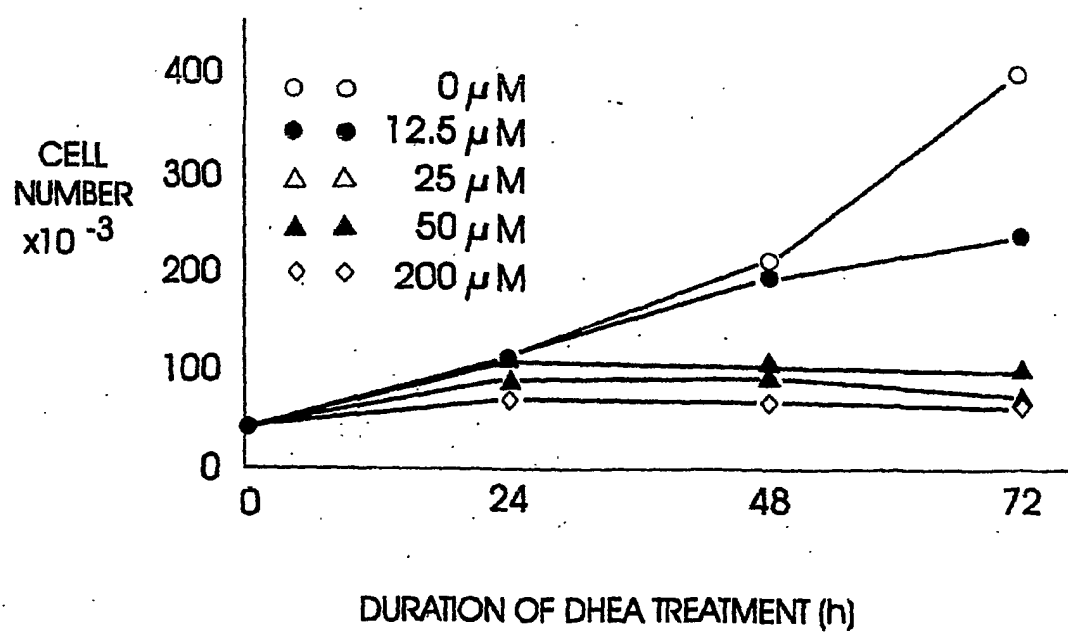
108. The method of claim 106, wherein the oligo(s) or the AIS is(are) administered as a respirable or inhalable formulation, optionally an aerosol of particle size about 0.05 to about 10 micron.

109. The method of claim 107, wherein the formulation comprises an oligo(s) or AIS of particle size about 0.1 micron to about 5 micron.

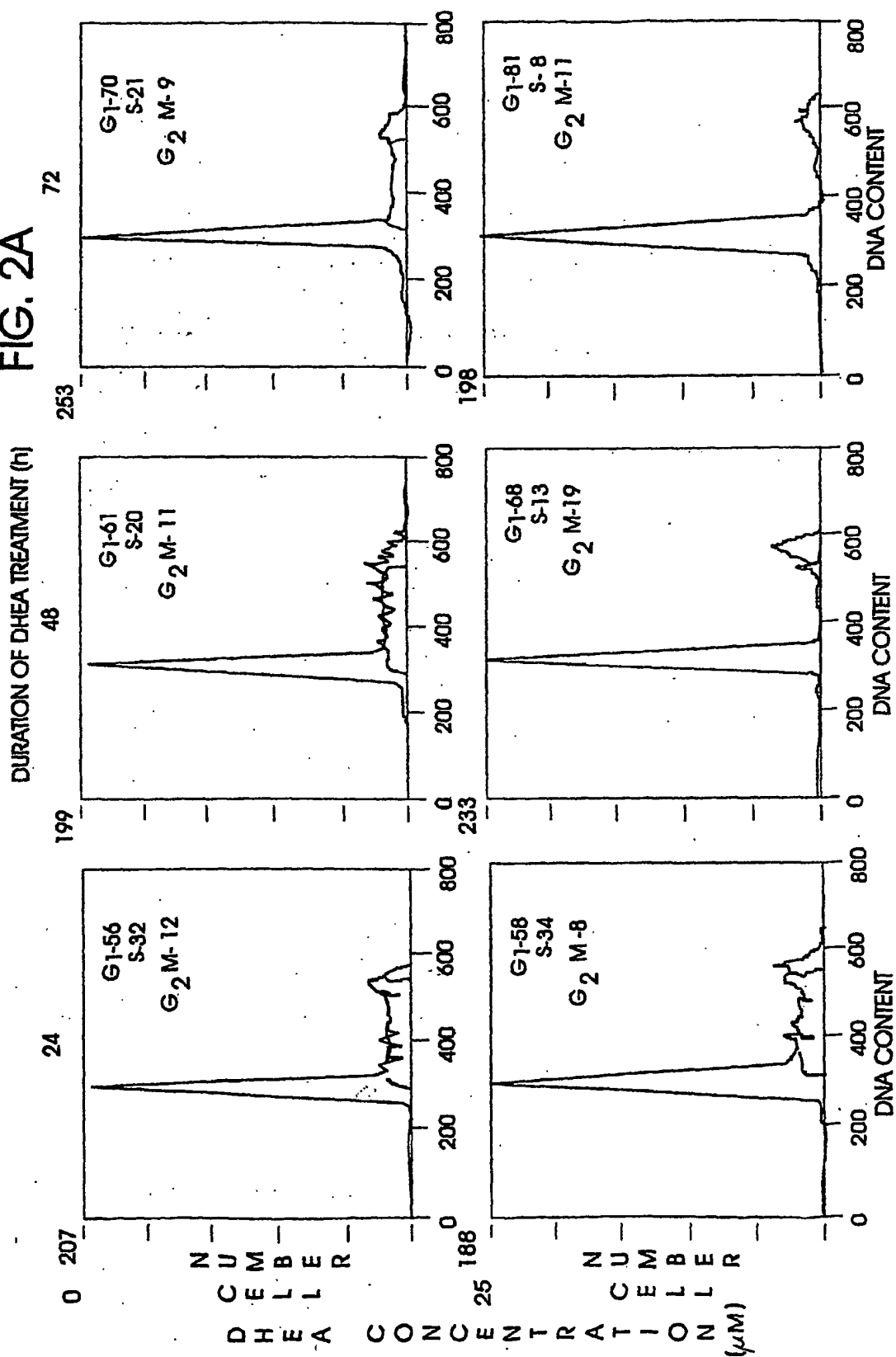
110. The method of claim 106, wherein the oligo(s) or the AIS is(are) administered nasally intrapulmonarily, optionally an aerosol of particle size about 8 to about 100 micron.

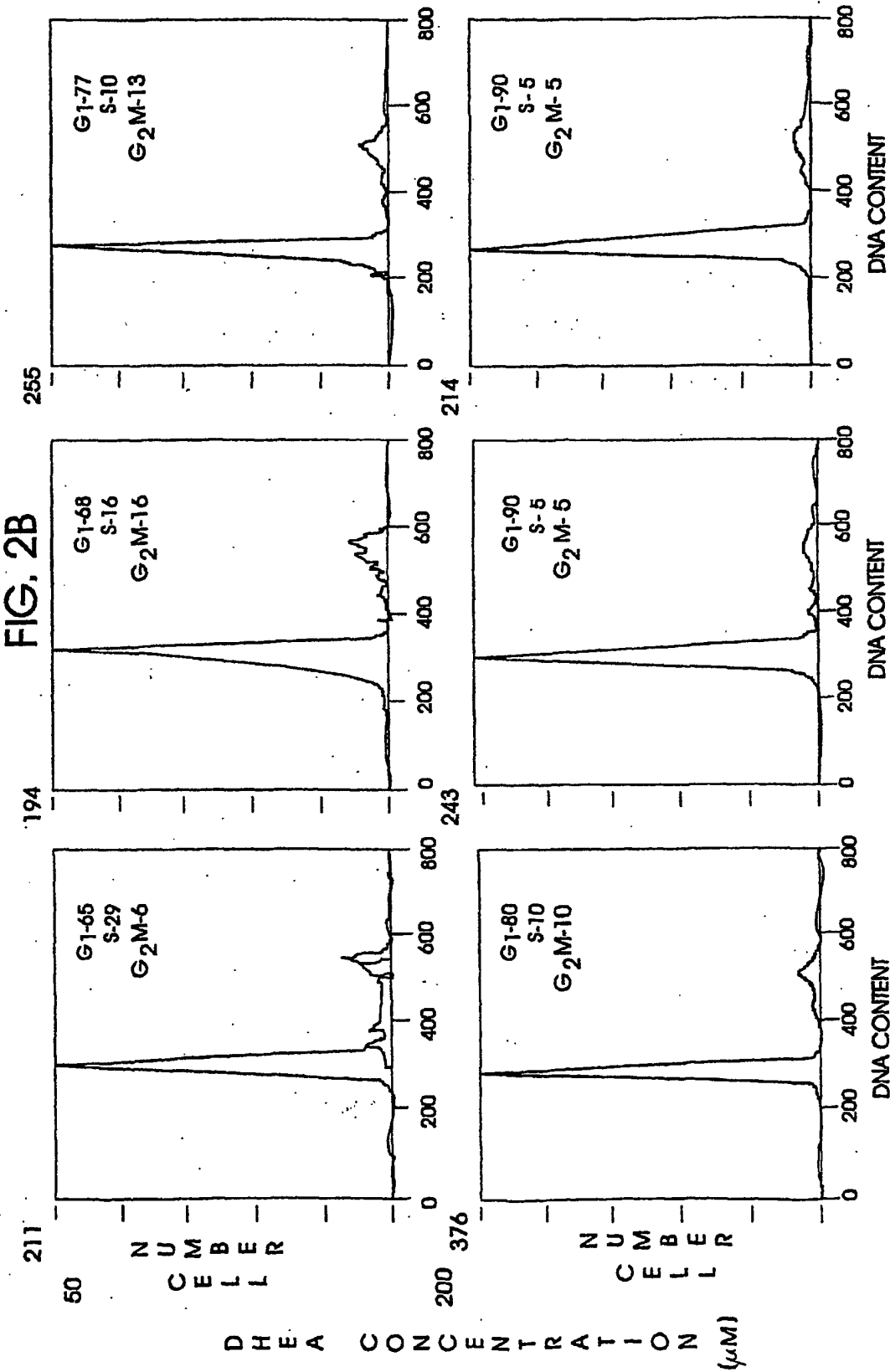
111. The method of claim 109, wherein the oligo(s) or the AIS has(have) a particle size about 10 to about 50 micron.

FIG. 1



**FIG. 2A**





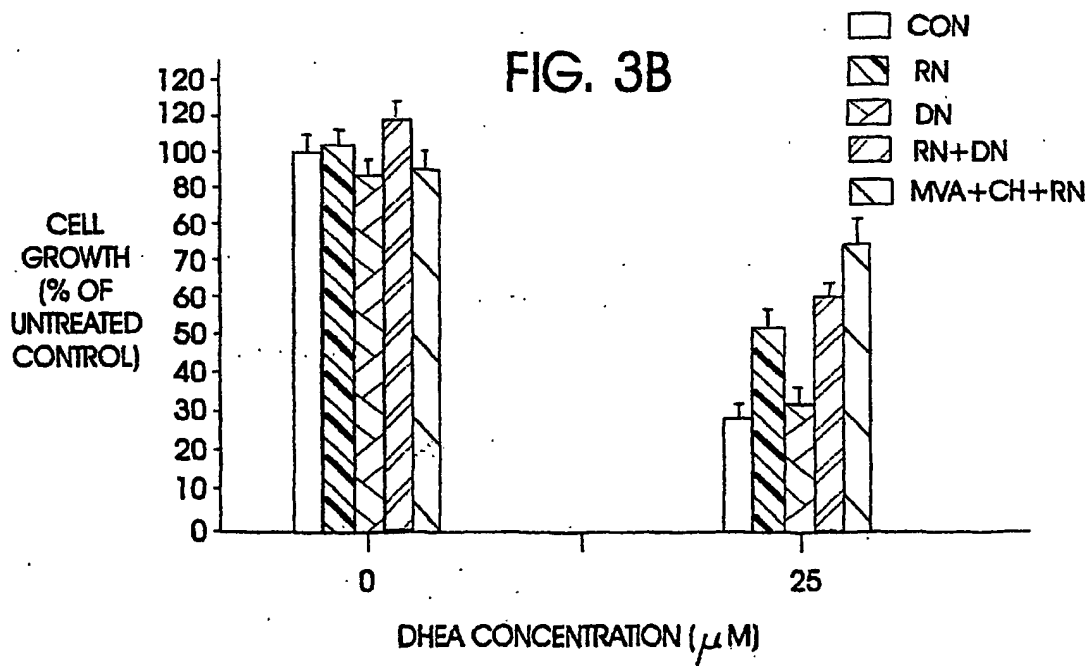
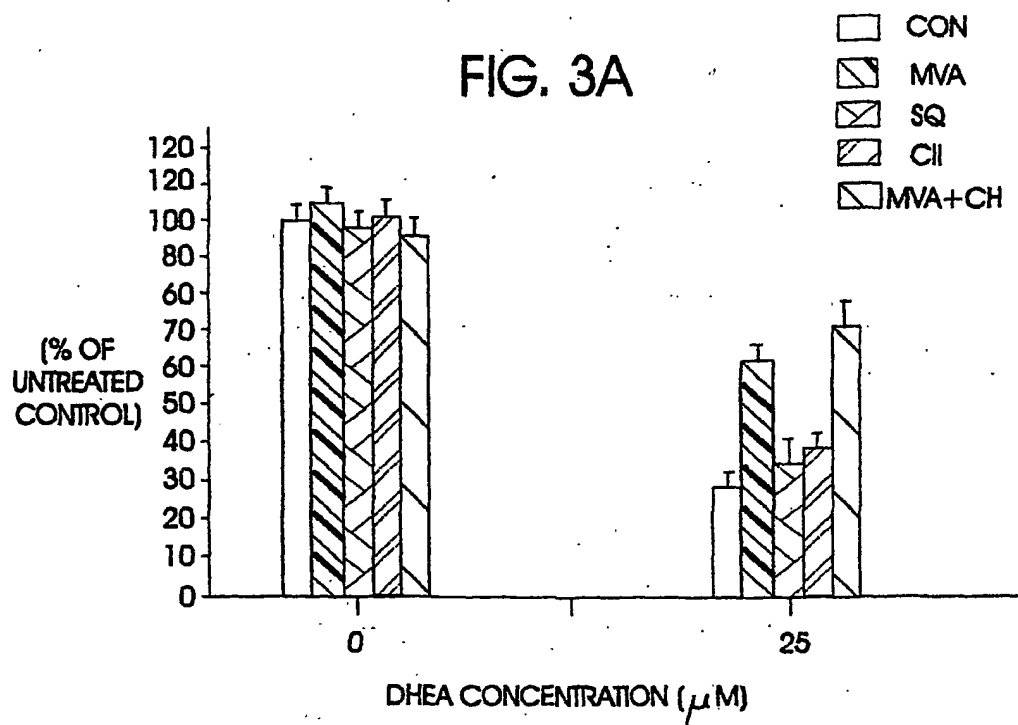


FIG. 4A

### DURATION OF TREATMENT

48h DHEA ( $\mu$ M)

FIG. 4B

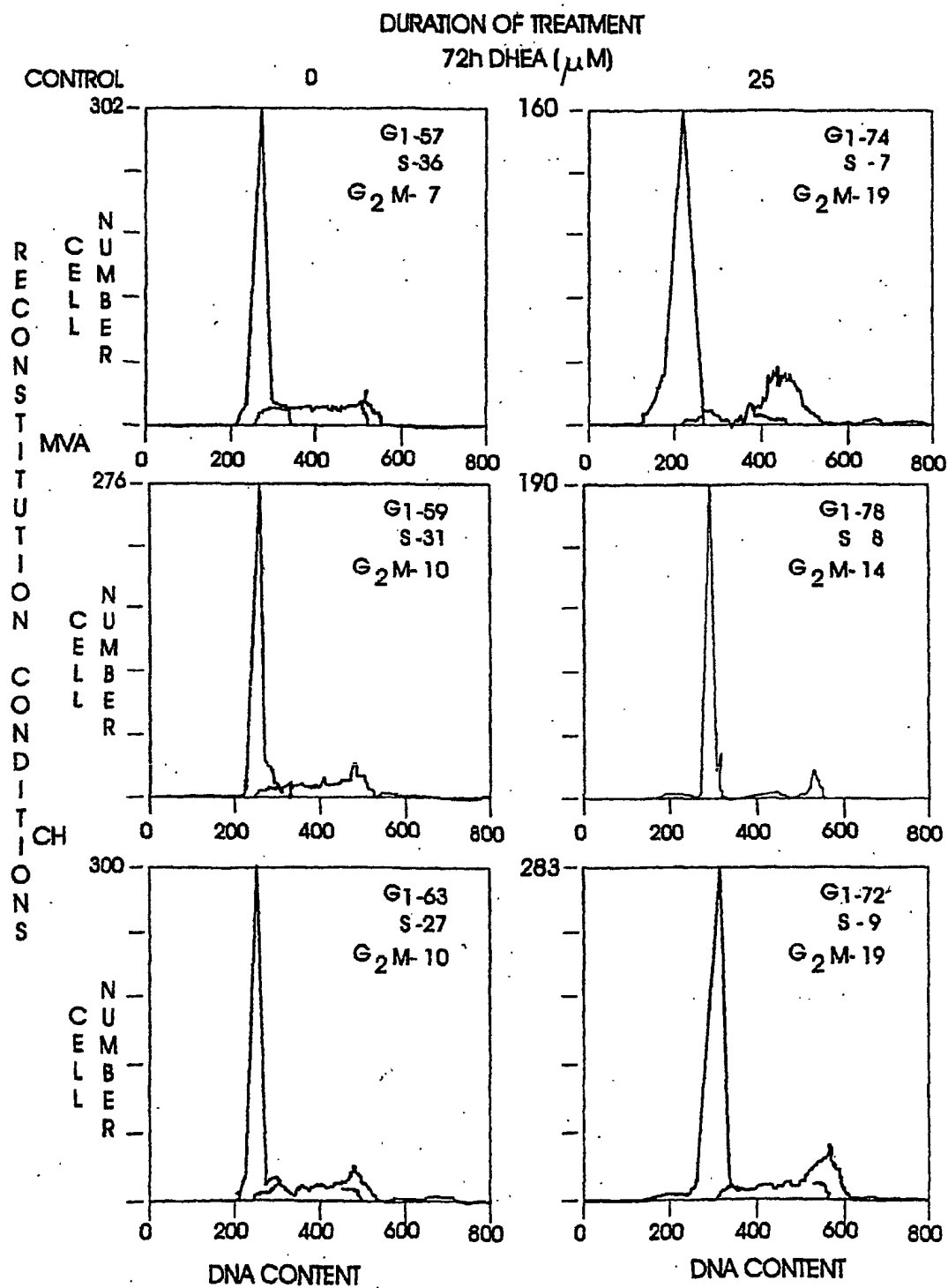




FIG. 4C

### DURATION OF TREATMENT

48h DHEA ( $\mu$ M)

RECONSTITUTION CONDITIONS

CELL NUMBER

DNA CONTENT

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MVA+CH

G1-55  
S-31  
G<sub>2</sub>M-14

0 200 400 600 800

MVA+CH

G1-65  
S-19  
G<sub>2</sub>M-16

0 200 400 600 800

MVA+CH+RN

G1-53  
S-32  
G<sub>2</sub>M-15

0 200 400 600 800

MVA+CH+RN

G1-67  
S-23  
G<sub>2</sub>M-10

0 200 400 600 800

RN

G1-49  
S-34  
G<sub>2</sub>M-17

0 200 400 600 800

RN

G1-64  
S-28  
G<sub>2</sub>M-8

0 200 400 600 800

FIG. 4D

### DURATION OF TREATMENT

72h DHEA ( $\mu$ M)

# RECONSTITUTION CONDITIONS

**CONTROL**

Q

25

272

230

NUMBER  
CELL

CELL

**MVA**

**G1-57**

S-32

G<sub>2</sub>M-11

**G1-74**

**S - 7**

G2M-19

205-

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100	100

CELL

CH

G1-59

**S-37**

G2M-9

174

G1-49

S- 20

G<sub>2</sub>M-11

205

NUMBER  
CELL

CELL

G1-53

**S-39**

G<sub>2</sub> M-8

175-

**G1-68**

**S-22**

**G<sub>2</sub>M-10**

## DNA CONTENT

### DNA CONTENT

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/13135

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 21/00; C12Q 1/68

US CL : 514/44; 536/24.5, 23.1, 25.1; 435/6, 325, 375

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/44; 536/24.5, 23.1, 25.1; 435/6, 325, 375

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CA, Biosis, West, Medline, SciSearch

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — A	US 6,096,722 A (BENNETT et al.) 01 August 2000 (01.08.2000). See entire document, particularly cols. 20, and 26	1, 3, 4, 40, 71 — 1-111
X — A	LANE, S.J. et al. Corticosteroid-resistant Bronchial is Associated with increased c-fos Expression in Monocytes and T Lymphocytes. Journal of Clinical Investigation. December 1998, Vol. 102, No. 12, pages 2156-2164, Abstract, 1st para of Intro, and page 2163, para. 3.	1, 3, 4, 40, 71 — 1-111

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"B" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

22 August 2002 (22.08.2002)

Date of mailing of the international search report

18 OCT 2002

Name and mailing address of the ISA/US

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